Genomics and Population Health 2005

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Centers for Disease Control and Prevention

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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For additional copies of Genomics and Population Health 2005, please visit our website at *www.cdc.gov/genomics/activities/ogdp/2005.htm*.

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Letter from the Director

Muin J. Khoury

Welcome to the second CDC report on genomics and population health. Since we published our first report, *Genomics and Population Health: United States, 2003*, the field of genomics has grown and so has the challenge of research translation.

During the past year, CDC has carried out the Futures Initiative (*www.cdc.gov/futures/*) with the intent of becoming a more efficient and customer-centric organization that achieves greater health impact. CDC created four new coordinating centers, including the Coordinating Center for Health Promotion (CoCHP). Because of the important contribution of genomics to diseases of public health significance, the Office of Genomics and Disease Prevention (OGDP) is now part of CoCHP. This change will allow us to continue to expand our efforts to integrate genomics into public health research and practice across CDC.

In 2004, CDC contracted with the Institute of Medicine (IOM) to conduct a workshop on the implications of genomics for public health. The summary of this workshop, entitled *Implications of Genomics for Public Health: Workshop Summary (2005)*, is now available online at *www.nap.edu/books/0309096073/html*. The summary defines **public health genomics** as "an emerging field that assesses the impact of genes and their interaction with behavior, diet and the environment on the population's health."

Public health genomics
An emerging field that assesses the impact of genes and their interaction with behavior, diet and the environment on the population's health.

CDC continues to collaborate with many partners in government, academia, professional organizations, consumer and community groups and the private sector to translate genomic advances for public health use. This report showcases these collaborations and CDC's continued work to improve population health in three major areas:

- Conducting public health genomics research.
- Evaluating genetic tests for practice.
- Integrating genomics into public health practice.

Conducting Public Health Genomics Research

In this section, *Chapter 1* discusses the potential value of human genomics in acute public health investigations (APHIs), which play a major role in public health efforts to control and prevent public health problems in communities. *Chapter 2* gives an update on the CDC Family History Public Health Initiative. *Chapter 3* focuses on current efforts to integrate genomics research into studies of vaccine safety. *Chapter 4* describes the impact of a Direct-to-Consumer (DTC) marketing campaign for genetic testing for breast and ovarian cancer susceptibility.

Evaluating Genetic Tests for Practice

The number of genetic tests available for clinical and public health practice is growing each year. *Chapter 5* reviews a model methodology, ACCE, developed by the Foundation for Blood Research to evaluate genetic tests in practice and summarizes results of its application to tests for *BRCA1*, *BRCA2* and *CFTR* mutations. *Chapter 6* describes a new CDC initiative that builds on the ACCE framework to develop and evaluate a sustainable process for Evaluating Genomic Applications in Practice and Prevention (EGAPP). *Chapter 7* discusses recommendations for adding cystic fibrosis to the newborn screening panel in state public health programs. *Chapter 8* highlights a national initiative to enhance availability, access and quality of genetic testing for rare diseases.

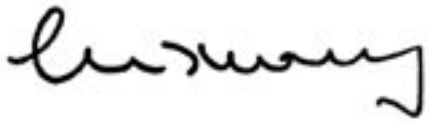
Integrating Genomics into Public Health Practice

CDC is partnering with several schools of public health and state health departments to demonstrate the integration of genomics into public health practice. *Chapter 9* presents an update on activities of three Centers for Genomics and Public Health. *Chapter 10* reports on the efforts of four state health departments to integrate genomics into public health programs. The appendices also offer additional Web resources and contact information for state genetic coordinators.

We would like to thank many individuals and programs for their contributions to this report. We hope that it will be useful in advancing the integration of genomics into public health research, policy, and practice. As always, your comments and suggestions are important to us; we invite you to fill out the comment card found at the end of this report, or visit our website at *www.cdc.gov/genomics/activities/ogdp/2005.htm*.

Best wishes in your endeavors as we continue to work together to expand the future horizon of public health genomics!

Sincerely,



Muin J. Khoury MD, PhD
Director, Office of Genomics and Disease Prevention, CDC

SNPets from CDC

NHANES Working Group
A CDC-wide team is currently collaborating with the National Cancer Institute to measure population variation in selected genes using stored DNA samples collected during the third National Health and Nutrition Examination Survey (NHANES) III.

Johnston County Osteoarthritis Project
CDC and the University of North Carolina are conducting a community-based cohort study of risk factors, including genetics, for osteoarthritis in a rural population.

National Birth Defects Prevention Study (NBDPS)
This ongoing case-control study has collected DNA samples by using cheek swabs from enrolled children and their parents, with over 5,000 samples received in 2004.

Surveillance for Duchenne/Becker Muscular Dystrophy (DBMD)
CDC is developing an approach to single gene disorders based on surveillance and improved screening, diagnosis and services, beginning with the Muscular Dystrophy Surveillance Tracking and Research Network (MD Starnet) in Arizona, Colorado, Iowa, and western New York state.

Analysis of Genetic Risk Factors for Fatal Influenza in Children
CDC is conducting a case-control study integrated with multi-state population-based surveillance for influenza-related hospitalizations in children during the 2004-2005 season to identify genetic variants that may put certain children at a greater risk of mortality associated with influenza.

Molecular Signatures of Cervical Neoplasia
As part of the National Cancer Institute's (NCI) Early Detection Research Network, CDC has detected and validated biomarkers that can be used to improve the sensitivity and specificity of cervical cancer screening.

The Role of Host Genetic Polymorphisms in Susceptibility to *M. Tuberculosis* Infection and Progression to TB Disease
CDC is working to identify genetic risk factors for susceptibility to TB. These could help TB programs in other countries target costly interventions to the 10% of exposed persons truly at risk of developing TB.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
CDC has assembled an independent, non-Federal working group of experts in epidemiology, genomics, public health, laboratory practice, medicine and health services to demonstrate an evidence-based review process for genetic tests in transition from research to clinical application.

Genetics of Kidneys in Diabetes (GoKinD) Study
CDC is developing a repository of DNA samples to study kidney disease in adults with type 1 diabetes as part of a study sponsored by the Juvenile Diabetes Research Foundation, in collaboration with the Joslin Diabetes Center and George Washington University.

CDC developed a 2004 summary briefing book to document its priorities, accomplishments, and future directions in human genomics. The following presents "snippets" from the briefing book; the complete document is available online at http://www.cdc.gov/genomics/activities/ogdp/2004/cochp_ogdp.htm.

Prevalence of Gene Variants Coding for Enzymes Involved in Nicotine and Carcinogen Metabolism
CDC will genotype approximately 7,300 samples from the NHANES III DNA Bank for genes associated with nicotine metabolism.

Chronic Beryllium Disease (CBD)
A sophisticated PCR-DNA sequencing assay has been developed to identify more precisely specific haplotypes associated with susceptibility to CBD.

Genetic and Environmental Factors in Brain Cancer
CDC is conducting a population-based case-control study to assess potential genetic susceptibility factors in the excess risk of brain cancer observed among persons working in agriculture.

Chapter 1

The Role of Human Genomics in Acute Public Health Investigations: Current Practice and Future Strategies

Mary Lou Lindegren, Shauna Lyn, and Cynthia Moore

Incorporating Human Genomics into Acute Public Health Investigations

Public health investigations are fundamental to the Centers for Disease Control and Prevention's (CDC's) mission to improve the health of the people of the United States. CDC has gained both national and global recognition for its rapid and effective investigations of acute adverse health events, which include **epidemiologic aids (Epi-Aids)**. CDC currently responds to approximately 80 to 100 Epi-Aid requests annually, and individual states together conduct 600 to 800 additional acute public health investigations (APHIs) annually. Although these studies generally focus on infectious diseases, they also investigate chronic diseases, environmental hazards, injuries, and occupational health.

Eidemiologic aid (Epi-Aid)
An epidemiologic field investigation of an urgent public health problem.

By collecting human genomic data, APHIs can potentially help in identifying additional risk factors for disease susceptibility, severity, and transmission. The results of such investigations could be used to:

- Characterize environmental exposures more accurately.
- Assess variation in disease outcomes.
- Assess the effectiveness and side effects of therapeutics and vaccines.
- Refine certain public health interventions, including vaccination, exposure reduction, chemoprophylaxis, behavioral modification, and education.

Examples of Investigations

Some examples of APHIs in which CDC collected human genomic data are as follows:

- An APHI in 1998 investigated leptospirosis among athletes at an Ironhorse Triathlon (1). Of the 887 triathletes included in the investigation, 98 were clinically ill with the disease. Analysis of *TNF-alpha* **polymorphism**

Polymorphism
Variants of a gene that are found in >1% of the population.

HLA (human leukocyte antigen) genes
Genes for cell surface proteins that vary among individual people and are important in immunity.

Vaccine adverse events (VAEs)
Symptoms or diseases that occur shortly after immunization and may be related to the administration of a vaccine.

and ***HLA* (human leukocyte antigen)** Class II genotypes (*DR*, *DQ*, *DP*) showed that triathletes who were *HLA DQ6* positive were more likely than those who were *DQ6* negative to have laboratory-confirmed leptospirosis. In addition, *DQ6*-positive triathletes who swallowed lake water had the greatest risk of developing the disease, an example of gene-environment interaction.

- Efforts are underway at CDC to study human genomic factors and **vaccine adverse events (VAEs)**. The emergence of myopericarditis following smallpox vaccination has highlighted the potential importance of human genomics in studying VAEs. The Clinical Immunization Safety Assessment (CISA) centers, a network of clinical academic centers in partnership with CDC, have a new initiative to evaluate VAEs, including human genomic factors (2). Human genomics may help in identifying risk for VAEs and in guiding the development of safer vaccines. *For more information on this topic, see Chapter 3, Genomics and Vaccine Safety: Research for Future Practice.*

- Approximately 35% of people exposed to tuberculosis (TB) develop latent infection, but only 2% develop active disease. CDC's Division of Tuberculosis Elimination (DTBE) (3), in collaboration with state partners, is studying human genomic factors in TB disease susceptibility, transmission, and outcome in the context of case contact investigations.

APHI Workshop Held in May 2004

During 2004, CDC, in collaboration with the Council of State and Territorial Epidemiologists (CSTE), formed a multidisciplinary APHI working group to outline key research priorities for incorporating genomics into APHIs and to develop the needed tools as outlined in the article that accompanied CDC's Genomics and Population Health: United States 2003 Report (4). The APHI working group held a meeting on May 12–13, 2004, inviting external consultants from the National Institutes of Health, state and local health departments, and academic medicine. The meeting participants had diverse expertise in the epidemiology of infectious and chronic diseases, occupational health, gene-environment interaction, laboratory genomic science, public health law, vaccine adverse events, bioinformatics, and population-based human genome epidemiology.

The goal of the meeting was to assist CDC and CSTE in developing a strategic plan for research priorities aimed at incorporating human genomics into APHIs at both the state and federal levels.

Conclusions from APHI Workshop

The external consultants who participated in the May 2004 APHI workshop generally agreed on the following:

- APHIs can provide unique opportunities to use genomic tools to analyze why clusters of individuals in communities become ill and to assess the impact of prevention and control strategies.
- Methodology (e.g., analytic, statistical); capacity (e.g., laboratory, specimen banking, bioinformatics); and ethical, legal, and social issues must be addressed.
- Research is needed to assess the value of genomics in improving the accuracy and effectiveness of investigations and the translation of results into public health interventions.
- Investigations that include genomics should be prioritized based on public health value, feasibility, resources, practicality, and community understanding.
- In high-priority investigations, consideration should be given to storing samples for future studies.
- Efforts should include the development of federal and state/local government, private, academic, and community partnerships.

Current Public Health Research Priorities

Since the conclusion of the APHI workshop in May 2004, CDC has been moving forward to incorporate human genomics into APHIs by creating a foundation for the following research priorities:

- Assessing and developing public health genomics infrastructure and capacity (including laboratory practice, analytic, informatics, banking, ethical/legal/social issues) and identifying gaps and needs.
- Synthesizing a relevant science base on human genomics and diseases/exposures.
- Identifying, developing, and applying appropriate analytical methods in epidemiology, statistics, laboratory practice, and bioinformatics.

- Developing standard language for informed consent for DNA sample collection, storage, and testing.

- Developing standard guidelines for the following procedures:
  – Specimen collection, processing, and transport.
  – Specimen banking.
  – Standardization of tools for data collection and management.

- Addressing education and training needs for constituents at all levels (i.e., CDC, states, communities, policy makers, media, and community partners).

- Creating partnerships with states to address the feasibility of APHIs, education, funding, and capacity.

- Developing mechanisms for sharing resources (e.g., templates, tools, laboratory support).

- Prioritizing investigations and conducting pilot studies in collaboration with state partners.

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Chapter 2
CDC's Family History Public Health Initiative: 2005 Update

Paula Yoon

In early 2002, the Centers for Disease Control and Prevention's (CDC's) Office of Genomics and Disease Prevention (OGDP), in collaboration with several other CDC programs and the National Institutes of Health (NIH), began an initiative to evaluate the use of family history information for the purpose of assessing a person's risk for common diseases and influencing early detection and prevention strategies. The major activities of this initiative include the following:

- Assessing existing strategies that use family history for disease prevention.
- Developing new tools for public health and preventive medicine.
- Developing a long-term research agenda and evaluation process.
- Developing and implementing public health campaigns and provider education.

A brief update of recent accomplishments in this initiative follows.

Family History for the Public

CDC has created a website (*www.cdc.gov/genomics/public/famhistMain.htm*) intended for the general public that contains fact sheets, slide presentations, case studies, news articles, links, and other resources.

U.S. Surgeon General's Family History Initiative

In 2004, CDC collaborated with the Surgeon General's Office, along with NIH, the Health Resources and Service Administration (HRSA), and other federal agencies, on a campaign to promote the use of family history for disease prevention and health promotion. The campaign calls for Americans to make Thanksgiving Day, a day that families traditionally gather together, the annual National Family History Day. A new tool, "My Family Health Portrait," can be downloaded from the campaign's website (*www.hhs.gov/familyhistory*) to facilitate the collection of family health history. The tool is also available in print and in both English and Spanish.

MMWR (Mortality and Morbidity Weekly Report)

As part of the effort to promote family history around Thanksgiving, CDC published findings from a recent survey in MMWR showing that although 96% of the public considered knowledge of one's own family health history important to one's personal health, only 30% of the public reported collecting health information from their relatives in order to develop a family health history (1).

Family Healthware™

The Web-based tool Family Healthware™, described in CDC's *Genomics and Population Health: United States 2003* report (2), has been completed and will be evaluated in a clinical trial that began in 2005. The tool collects information about health behaviors, use of screening tests, and health history of a person's first- and second-degree relatives for the following six diseases: coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer. The software includes algorithms that process the family history data and provide a qualitative assessment of familial risk (strong, moderate, or weak) for each of the six diseases. Another set of algorithms provides recommendations for lifestyle changes and screening tests that are based on a person's reported health behaviors and family history. A printable report includes a pedigree drawing of the family tree, a summary of familial risk for each disease, and personalized prevention recommendations.

Evaluation Study

Beginning this year, three research centers (University of Michigan School of Medicine, Evanston Northwestern Healthcare Research Institute, and Case Western Reserve University School of Medicine) will conduct a study to evaluate the clinical utility of Family Healthware™. The study, consisting of approximately 8,400 patients aged 35–65 years who attend primary care practices, will determine whether family history risk assessment and personalized prevention messages influence health behaviors and use of medical services.

Public Health Research

Family history has been shown to be an independent risk factor for diseases in many research studies, but a systematic evaluation of the validity and utility of family history information for risk assessment and disease prevention on a population basis has not been done. We are currently conducting in-depth analyses of family history as a risk factor for diabetes, heart disease, and cancers using existing data sets (i.e., Healthstyles; National Health and Nutrition Examination Survey; National Cancer Institute Colon Cancer Family Registry; National Heart, Lung, and Blood Institute Multi-Ethnic Study of Atherosclerosis) as well as association studies of family history and preventive behaviors (e.g., diet, exercise, screening). CDC is also working with researchers and public health

programs to improve the quality of family history data by developing standard family history questions and modules for national and state-based health surveys, including the Behavioral Risk Factor Surveillance System.

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Chapter 3

Genomics and Vaccine Safety: Research for Future Practice

Robert L. Davis

Need for Vaccine Safety Research

Each year, more than four million children are born in the United States. Parents naturally want to protect their children as much as possible from disease and illness. One of the most effective ways to accomplish this goal is for children to receive immunizations according to the recommended vaccination schedule (1). During 2001, almost 80% of children aged 19-35 months of age living in the United States received **vaccine** coverage for DTP/DT/DtaP, poliovirus, and measles.

Vaccines
Preparations of killed or modified bacteria or viruses meant to stimulate an immune response to ward off future disease.

Throughout the United States and other countries, however, vaccine safety concerns have increased. Popular media, including parenting magazines, have discussed purported associations of vaccines with negative health effects, such as **autism** and inflammatory bowel disease, as well as the potential negative health effects of vaccine preservatives (e.g., **thimerosal**) on neurological development. These negative reports are often widely believed, despite the lack of solid evidence. Both public health professionals and physicians are frequently called upon to assure parents that a relationship between vaccinations and neurodevelopment disorders has not been established, although due to insufficient data, the absence of such an association has not been confirmed either. Whether certain people may be at increased risk for adverse effects from vaccination because of an underlying health condition or because of their individual genetic make-up is an important area for research.

Autism
A childhood disorder of unknown etiology characterized primarily by profound deficits in communication and social interactions.

Thimerosal
A mercury-containing organic compound that was widely used until recently as a preservative in vaccines.

Current Vaccine Safety Research at CDC

The Centers for Disease Control and Prevention (CDC) has three major components for vaccine safety monitoring and research:

- *Vaccine Adverse Events Reporting System (VAERS)*. *VAERS* is a nationwide passive reporting system for voluntary reports of adverse events that are suspected of being related in some way to vaccination.

- *Vaccine Safety Datalink project (VSD)*. *VSD* is a large collaborative project that links data from eight managed care organizations (MCOs) in the

United States, covering approximately 3-4% of the U.S. population (2,3). The automated databases from these MCOs can be used to link vaccinations to outcomes, including subsequent visits for symptoms or illnesses that are evaluated in outpatient settings, emergency departments, or hospitals. A particularly strong component of VSD is its coverage of millions of enrolled subjects, allowing for the study of rare events that might follow immunization. Typically, VSD contains information necessary for rigorous epidemiologic studies, including numbers of vaccine doses administered, comparison groups, and individual-level data on potentially confounding variables.

- *Clinical Immunization Safety Assessment (CISA) network*. *CISA* is a new initiative created to fill the need for individualized evaluations of patients with specific vaccine-associated adverse events or with specific immunization-related needs. CISA is a network of clinical academic centers that work in partnership with CDC to improve scientific understanding of vaccine safety at the individual patient level, providing clinical expertise in evaluating and treating adverse events following immunization.

Integrating Genomics Into Vaccine Safety Studies

Currently, both VSD and CISA are working toward integrating genomics into studies of vaccine safety. Two examples of these studies are as follows:

Myopericarditis
Inflammation of the heart muscle and the membrane surrounding it.

- *CISA study of myopericarditis*. The primary goal of this study is to define prospectively the incidence of **myopericarditis** following vaccination in 600 enrolled subjects receiving smallpox vaccination and 200 persons receiving influenza vaccination. The study will also assess inflammatory markers (cytokines and other immune factors) in vaccinees who develop clinical or subclinical myopericarditis in comparison with asymptomatic vaccinees (controls).

  In collaboration with the National Institutes of Health (NIH), funding for this study has been substantially increased to collect, transport, and store DNA, RNA, and blood mononuclear cells from all smallpox vaccines and controls for genetic analyses and detailed evaluation of the immune response in cases and controls.

Rheumatoid arthritis (RA)
A chronic disease characterized by joint inflammation.

- *VSD study of rheumatoid arthritis*. VSD includes an ongoing genetic substudy of **rheumatoid arthritis (RA)** following hepatitis B vaccination (HBV). The goal of this study is to determine whether a genetic predisposition to developing RA exists following HBV. Interactions between genes and other genetic polymorphisms and HBV in the development of RA will be examined in a case-only study of RA cases from CDC's

VSD project. The case-only study design is highly efficient, because the distribution of HLA (human leukocyte antigen) gene variants in the population is not expected to vary with HBV exposure.

The impetus for this study originated with reports to VAERS between 1991 and 1998 of 39 persons with RA following HBV vaccination. Data analysis suggested a twofold increase in the rate of possible RA in HBV recipients compared with the rate in influenza vaccine or pneumococcal polysaccharide vaccine (PPV) recipients. Among RA cases reported to VAERS, the mean time from vaccination to onset of symptoms was 3.6 days (range: 0–9 days). The mean age of the reported RA cases was 41 years (range: 18–58 years). Other non-RA rheumatic conditions were also reported, including systemic lupus erythematosus (SLE), gout, and reactive arthritis. Despite the limitations of a passive reporting system, such as VAERS, this analysis suggests an increased rate of RA following HBV compared with PPV or influenza vaccination.

These data prompted the VSD to develop a protocol to determine whether HBV increases the risk of chronic joint disease. All persons aged 15 to 59 years with continuous MCO membership from January 1, 1995 to December 30, 1999 were eligible, and those with an automated record diagnosis of RA were selected for further medical record review. RA cases were confirmed by using the 1987 American College of Rheumatology criteria and a rheumatologist's chart review. To date, blood samples have been collected from more than 300 subjects with confirmed or likely RA for evaluation of HLA status. In addition, a study will be conducted on a number of polymorphisms recently found to be risk factors for developing RA, such as the *PTPN22* SNP as well as other **SNPs** in this gene/region.

SNPs
Single nucleotide polymorphisms.

The Future of Genomics and Vaccine Safety

The study of the genomics of vaccine safety is in its infancy. The creation and maintenance of large collaborative projects are needed to allow collection of the necessary information (including DNA) from large numbers of people. In the future, a greater understanding of population-wide genetic variation will allow the delivery of safer and more efficacious vaccines, and may allow for the personalized delivery of specific vaccines.

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Chapter 4

Direct-To-Consumer Marketing Campaign: Genetic Testing for Susceptibility to Breast and Ovarian Cancer

Melanie F. Myers and Cynthia Jorgensen

Introduction

Genetic testing
Processes or methods used to analyze human DNA, RNA, genes, chromosomes, proteins, or metabolites in order to detect mutations, chromosomal changes, karyotypes, phenotypes and/or expression pattern variation.

Genetic testing for susceptibility to breast and ovarian cancers is used to search for variants of the ***BRCA1*** and ***BRCA2*** genes that have been associated with cancer in high-risk families. Women who inherit one of these variants have an increased risk of developing breast or ovarian cancer during their lifetime. Most cases of breast and ovarian cancers are not associated with variants in the *BRCA1* or *BRCA2* genes, and the genetic test has not been recommended for routine screening (1,2). *For more information on this topic, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2, and CFTR.*

BRCA1* and *BRCA2
Inherited alterations in the genes, called BRCA1 and BRCA2 (short for Breast Cancer 1 and Breast Cancer 2), are involved in some cases of hereditary breast and ovarian cancers.

The Direct-to-Consumer Marketing Campaign

Despite the limited applicability of the test to the general population, the sole U.S. provider of clinical *BRCA1* and *BRCA2* testing, Myriad Genetic Laboratories, Inc.*, began a pilot **direct-to-consumer marketing (DTC)** campaign in September 2002. The pilot campaign was conducted for 5 months in two cities (Atlanta, Georgia, and Denver, Colorado). The stated intent of the campaign was to raise awareness among women aged 25-54 years with personal or family histories of breast and ovarian cancers; in addition, the campaign was intended to help motivate these women to speak with their health care providers about their personal risk for hereditary breast and ovarian cancers, and to help them find out how a genetic test could help assess and manage their risk (3). Although DTC advertisements for pharmaceuticals have appeared in the mass media for the past 20 years, DTC advertisements for genetic testing have only recently appeared in the mass media and on the Internet (4).

Direct-to-consumer (DTC) marketing
Advertisements that appear in mass media publications, including television and the Internet, which are targeted directly to consumers.

Elements of the campaign included (3):

- *Physician launch mailer,* which was sent to physicians in August 2002 to inform them about the campaign.

- *Television commercial*, which was aired to consumers during prime daytime, early morning, prime access, and early and late fringe from September 2002 to January 2003.

** Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.*

- *Print advertisements*, which appeared from October 2002 to February 2003 in women's magazines, including home, health, entertainment, and regional magazines and newspapers.

- *Red Flags program*, in which materials, including posters, patient brochures, and cancer history tear-off pads for use in medical offices, were mailed to physicians to help patients self-assess their risk for hereditary cancers.

- *Toll-free number and website*, for health care providers and patients to obtain more information.

Public Health Significance

The DTC campaign for genetic testing for inherited breast and ovarian cancer susceptibility is of public health significance for the following reasons:

- Interpretation of the test is complex.

- The test is not appropriate for most women.

- This is the first time an established genetic test has ever been marketed directly to the public through mass media, and it may serve as a prototype for future DTC marketing of genetic tests.

The Complexity of *BRCA1* and *BRCA2* Testing

Results of *BRCA1* and *BRCA2* testing can only be interpreted in the context of family history. An affected person usually must first be tested to determine whether a *BRCA1* or *BRCA2* mutation can be identified within the person's family. Only if a mutation is identified will testing unaffected family members be informative for predicting their cancer risk. Both *BRCA1* and *BRCA2* mutations are not found in all women with family histories of breast or ovarian cancer, and not all women who have a *BRCA1* or *BRCA2* mutation will develop either breast or ovarian cancer (2,5).

BRCA1 and *BRCA2* Tests Are Not Appropriate for Most Women

Most breast and ovarian cancers occur in women who have no family histories of either of these cancers or only a single affected relative. *BRCA1* and *BRCA2* mutations occur in approximately 1 in 400 women and account for, at most, 5%–10% of all cases of breast and ovarian cancers; there are probably other, as yet unidentified, inherited breast cancer susceptibility genes (1,2,5).

Direct-To-Consumer Advertising

DTC advertising of prescription medications and medical tests have proliferated during the past decade. Advocates of DTC advertising argue that it can play an important role in improving the public's health by educating consumers about health conditions and increasing the public's use of appropriate medications and treatments (6). Opponents, however, believe that DTC advertising leads to misconceptions about the health benefits of tests and medicines among consumers (7) and results in the use of more expensive, but not necessarily more effective, drugs and tests (8).

The DTC campaign for breast and ovarian cancer susceptibility marked the first time that an established genetic test was marketed directly to the public, and it may serve as a prototype for future DTC marketing of genetic tests. Because of the complexities surrounding genetic testing, however, it is unclear whether the medical and public health communities are prepared to handle the challenges accompanying an increase in DTC marketing of genetic tests (9).

Public Health Response

An investigation to monitor the impact of the DTC campaign was conducted at the request of state epidemiologists and public health officials in the two pilot cities where the campaign took place (Atlanta, Georgia, and Denver, Colorado) as well as in two control cities (Raleigh-Durham, North Carolina, and Seattle, Washington). The investigation was a joint effort of the four states, the Office of Genomics and Disease Prevention, and the Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Control, Centers for Disease Control and Prevention. Because the campaign was scheduled to end in February 2003, a rapid public health response was required.

Survey Development

Two working groups developed two separate surveys to ask providers and consumers about genetic testing for susceptibility to breast and ovarian cancers.

The consumer survey assessed:

- Awareness about genetic testing for risk of breast and ovarian cancers among women aged 25-54 years in the two cities targeted by the campaign as well as in two cities not targeted by the campaign.
- Self-reported knowledge about this type of genetic testing, by city.
- Respondent characteristics that influence awareness and knowledge of genetic testing for risk of breast and ovarian cancers.

The consumer survey was a programmed telephone survey of randomly selected women aged 25-54 years in four cities. The survey consisted of 51 questions and was conducted between April 21 and May 20, 2003.

The provider survey assessed:

- Physicians' knowledge and awareness about genetic testing for breast and ovarian cancer risk.

- Physicians' perceptions of patient demand for information about this type of genetic testing.

The provider survey, which included 35 questions and a $50 incentive, was mailed to randomly selected physicians in four specialties: family practice, internal medicine, obstetrics/gynecology, and oncology. The initial mailing was conducted on May 1, 2003.

Consumer Survey Results

A total of 1,635 consumer telephone surveys were completed (overall participation rate was 45%; participation rate in Atlanta was 56%; Denver, 42%; Raleigh-Durham, 39%; Seattle, 43%). The average age of respondents was 40 years old. The majority of respondents were white, married, had higher than a 12th-grade education, and had an income greater than $35,000. Overall, 13% of respondents had a first-degree relative with breast or ovarian cancer.

Respondents in the pilot cities were twice as likely as respondents in the control cities to report seeing or hearing an advertisement on television, radio, or in a magazine about a test to determine a woman's risk for breast or ovarian cancer. Self-reported levels of knowledge about genetic testing for breast and ovarian cancers did not differ between the pilot and control cities (Table 1). These findings were similar after stratifying by race, education, and income, although education was positively associated with the self-reported level of knowledge.

Among consumers in all cities, those with a first-degree relative with either breast or ovarian cancer were slightly more likely to recall being exposed to an advertisement about genetic testing for breast or ovarian cancer risk and to report higher levels of knowledge about genetic testing.

Table 1. Consumer Awareness and Knowledge of Genetic Testing for Breast and Ovarian Cancer Susceptibility**

Question	Response Choices	Denver % (N=401)	Atlanta % (N=410)	Raleigh % (N=403)	Seattle % (N=421)
Saw/heard an advertisement about a genetic test to determine a woman's risk for breast or ovarian cancer in the past 6 months[†]	Yes Not yes**	36 (144) 64 (257)	42 (172) 58 (238)	23 (91) 77 (312)	12 (50) 88 (371)
How would you describe your knowledge about genetic testing for breast and ovarian cancer?[§]	Little/nothing Some A lot***	68 (274) 29 (117) 2 (9)	70 (285) 28 (114) 2 (10)	73 (294) 25 (99) 2 (8)	69 (289) 27 (114) 4 (16)

**Some missing values are included.
***Sum of percentages is not always 100 because of "don't know" responses. Missing values are excluded.
[†]χ^2 value = 112.3; P <.001.
[§]χ^2 value = 5.6; P = .47.

Provider Survey Results

In all, 1,054 (66%) provider questionnaires were returned and analyzed. Most respondents were male, had been in practice more than 10 years, and saw fewer than 100 patients per week.

In general, provider knowledge about the inheritance of breast and ovarian cancer risk did not differ between the pilot and control cities (Table 2). The majority responded correctly that a woman with early onset breast cancer was more likely to have inherited a *BRCA1* or *BRCA2* variation than a woman who was affected at a much later age. Oncologists and obstetricians/gynecologists were more likely than family practitioners and internists to know that a *BRCA1* or *BRCA2* variation can be inherited from either parent and that a healthy woman who has a sister with a known *BRCA1* variation has a 50% chance of inheriting the same variation.

Providers in the pilot cities were significantly more likely than providers in the control cities to report having seen or heard, or having patients mention that they had seen or heard, an advertisement promoting genetic testing for breast and ovarian cancer risk in the popular media (Table 2).

Providers were asked to indicate on a 5-point scale how relevant it would be to their practice to learn more about genetic testing for breast and ovarian cancer risk (1 = "not at all relevant" to 5 = "extremely relevant"). The mean rank was 3.5 across all specialties, indicating that most providers felt that gaining this knowledge would be relevant to their practice. Internists were less likely to rank this knowledge as relevant than the other specialties (mean rank = 3.1).

Table 2. Provider Knowledge of Genetic Testing for Breast and Ovarian Cancer Susceptibility and the DTC Campaign by City**

Question	Response Choices	Denver % (N=270)	Atlanta % (N=292)	Raleigh % (N=164)	Seattle % (N=328)
How likely is a woman who gets breast cancer at an early age to have inherited a BRCA1 or BRCA2 variation compared to a woman who gets breast cancer at a much later age?†	More likely	84 (222)	79 (225)	80 (127)	88 (285)
	Equally likely	5 (12)	4 (10)	5 (8)	2 (8)
	Not sure	11 (30)	18 (50)	15 (24)	10 (31)
Women can inherit a BRCA1 or BRCA2 variation from: §	Either parent	55 (146)	52 (147)	43 (68)	52 (171)
	Mother only	12 (31)	17 (47)	21 (34)	16 (53)
	Not sure	33 (87)	31 (88)	36 (57)	32 (103)
What is the chance that a healthy woman who has a 30-year-old sister with a known BRCA1 variation has inherited the same BRCA1 variation?¶	25%	22 (58)	29 (81)	21 (33)	25 (80)
	50%	48 (128)	42 (119)	49 (78)	46 (150)
	75%	3 (8)	2 (5)	2 (3)	1 (4)
	Not sure	27 (70)	27 (77)	28 (45)	28 (89)

Question	Response Choices	Denver % (N=270)	Atlanta % (N=292)	Raleigh % (N=164)	Seattle % (N=328)
Personally saw/ heard an ad about genetic testing for breast/ovarian cancer risk in the past 6 months***	Yes No Not sure	39 (103) 55 (147) 6 (15)	44 (126) 51 (146) 5 (15)	29 (47) 66 (107) 6 (9)	18 (59) 76 (250) 6 (18)
Patients mentioned they had seen/ heard an ad for breast/ ovarian cancer risk in the past 6 months††	Yes No Not sure	28 (74) 68 (178) 4 (11)	27 (78) 67 (191) 6 (17)	10 (16) 87 (140) 3 (5)	8 (26) 99 (286) 4 (12)

**Sum of percentages is not always 100 because of rounding.
† Excludes missing values and five respondents who answered "less likely"; χ^2 value = 12.9; P=.045.
§Excludes missing values and one individual who answered, "father only"; χ^2 value = 9.9; P=.13.
¶Excludes missing values and four individuals who answered "100%"; χ^2 value = 7.8; P=.55.
***χ^2 value = 55.7; P <.0001.
††χ^2 value= 66.8; P <.0001.

Additional findings are reported in a 2004 issue of MMWR (10).

Conclusions

By responding relatively rapidly to the campaign with surveys of consumers and providers, states were able to monitor the campaign's effects on the participants' awareness, knowledge, and perceptions. Findings from this investigation indicate that the DTC campaign for genetic testing for breast and ovarian cancer susceptibility increased awareness about inherited susceptibility to breast and ovarian cancers in the pilot cities. The DTC campaign suggests that women who are interested in learning more about *BRCA1/2* testing should consult their health-care providers. Findings from this study indicate that providers in different specialties are not equally knowledgeable about *BRCA1/2* testing, however, and that many providers are not adequately prepared to respond to their patients' questions about *BRCA1/2* testing. Most providers reported that information about inherited breast and ovarian cancer susceptibility testing would be relevant to their practice. These findings suggest a need for more professional education about genetic testing in general, as well as specifically for inherited susceptibility to breast and ovarian cancer risk.

The Food and Drug Administration (FDA) does not currently regulate most DNA-based tests, including the *BRCA1/2* test (9). Better understanding of the public health impact of DTC marketing of DNA-based tests requires a strategy that includes data collection for the purpose of investigating test utilization and access. Collaboration between public health agencies, clinical care providers, professional organizations, and industry (e.g., biotechnology companies, and laboratories) will be needed to collect these data. Information obtained through these collaborations could serve as a model for future public health responses as genomics becomes more integrated into health care and disease prevention.

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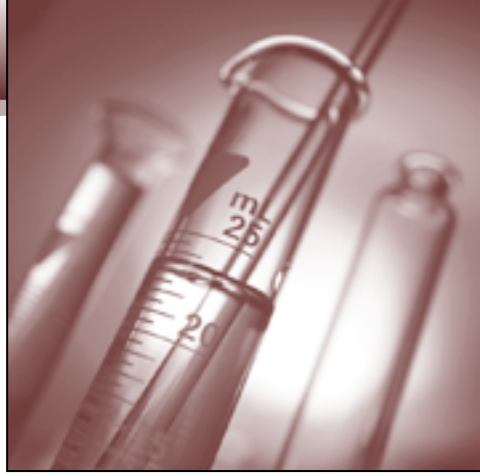


Chapter 5
ACCE Reviews of Genetic Tests: *BRCA1*, *BRCA2*, and *CFTR*

Glenn E. Palomaki, Monica R. McClain, and James E. Haddow

Introduction to ACCE

ACCE is a model process for evaluating data on emerging genetic tests. It was developed by the Foundation for Blood Research through a cooperative agreement with the Centers for Disease Control and Prevention (CDC) (1). The ACCE review process builds on previously published methodologies and terminology introduced by the Secretary's Advisory Committee on Genetic Testing. The purpose of the ACCE format is to help policy makers make decisions using up-to-date and reliable information.

The acronym **ACCE** stands for the four key elements needed to evaluate any genetic test: **A**nalytic validity; **C**linical validity; **C**linical utility; and **E**thical, legal, and social implications.

- *Analytic validity* defines the ability of a test to measure the genotype of interest both accurately and reliably.
- *Clinical validity* defines the ability of a test to detect or predict the associated disorder (i.e., phenotype).
- *Clinical utility* defines the risks and benefits associated with the introduction of a test into practice. Specifically, clinical utility focuses on the health outcomes, both positive and negative, associated with testing.
- *Ethical, legal, and social implications* of the testing process include those inherent in any medical technology as well as those specific to genetic tests.

The ACCE Review Process

ACCE review differs from other evidence-based methods (e.g., those used by the U.S. Preventive Services Task Force) in that the ACCE review process is:

- Less formal (e.g., structured criteria are not always used to assess and describe the quality of the studies).

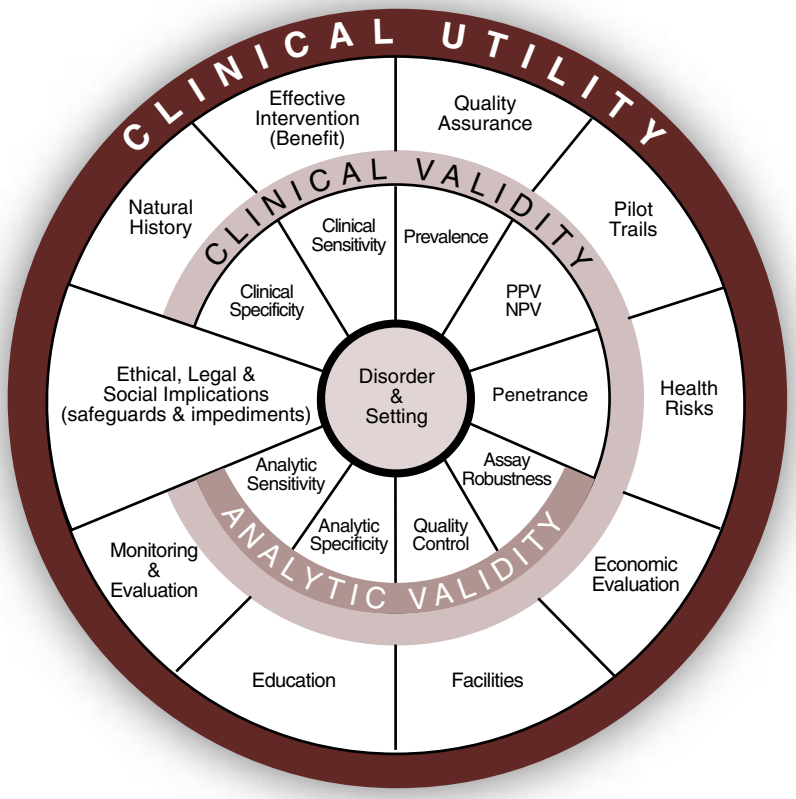
- More comprehensive (e.g., includes evaluation of assay validation and performance).
- More focused on issues associated with genetic testing.

The first step in the ACCE process is to determine the following:

- What disorder to test for, and in what setting.
- What clinical scenario to select (i.e., who is to be tested and the setting in which the testing will occur).
- What test (or tests) should be used in the clinical scenario.

The next step is an in-depth process that includes identifying, collecting, evaluating, interpreting, and reporting data about the DNA (and related) tests. A list of 44 questions forms the basis of the analytic framework. An important by-product of this process is the identification of the knowledge gaps.

The ACCE wheel, as pictured below, shows the relationships between testing components and selected topics covered within those components.



The following sections in this chapter focus on selected findings from two of the five clinical scenarios that were examined in depth as part of the *ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests* project. More information is available in print form (1) as well as on the CDC website at *www.cdc.gov/genomics/gtesting/ACCE.htm*.

Family History and *BRCA1* and *BRCA2* Mutation Testing to Identify Women at Risk for Inherited Breast/Ovarian Cancer

Several professional organizations and governmental entities in the United States, Europe, and Australia recommend the routine collection of family health history pertaining to breast and ovarian cancers as a way of identifying families in which inherited forms of these cancers may exist (2-4).

The ACCE project reviewed the ability of family health histories and subsequent *BRCA1* and *BRCA2* mutation testing to help prevent breast and ovarian cancers. In addition, both were then examined for their potential from a public health perspective. One important result of this review was the insight gained on how to integrate important parameters commonly provided to patients/public health professionals into one consistent, interrelated framework that could be used to refine published estimates (5). Example 1 shows estimates based on epidemiologic data commonly provided to patients or public health professionals.

Example 1. Estimates of Epidemiological Data Commonly Given to Patients/Public Health Professionals

Cumulative incidence of cancer is often provided for a specific age (e.g., by age 70) and is the proportion of women within a given population that is expected to develop breast cancer by that age. **Approximately 1 in 10 women will develop breast cancer by age 70 (6).**

Mutation prevalence is a measure of how often mutations in the *BRCA1* or *BRCA2* gene occur in an unselected group of women. Only a few studies have addressed mutation prevalence for these genes and have done so indirectly. **Approximately 1 in 300 to 1 in 450 women have a mutation in the *BRCA1* or *BRCA2* gene.**

Clinical sensitivity is the proportion of women with a *BRCA1* or *BRCA2* mutation among breast cancer cases. Because most breast cancer cases are sporadic, estimated clinical sensitivity is low. **Reports range widely from 2% to 10% of breast cancer cases by age 70.**

Penetrance is defined as the proportion of women with a mutation in the *BRCA1* or *BRCA2* gene that will develop breast cancer by a given age. **Published penetrance estimates vary from 35% to 80% by age 70.**

In general, most published studies have focused on only one or two of these parameters simultaneously; however, more reliable results for each can be computed if they are considered together and integrated into one consistent, interrelated framework.

Example 2 shows internally derived, consistent values for four of these interrelated parameters (5). The "reasonable ranges" are less broad than the range of estimates contained in the published literature (*see Example 1*), particularly for clinical sensitivity and penetrance.

Example 2. Internally Consistent Estimates of Epidemiological Data

- *Cumulative incidence* of breast cancer by age 70: 9.7% (approximately 1 in 10 women).
- *Mutation prevalence* for *BRCA1* and *BRCA2* in the general population: 1:380 (reasonable range: 1:310 to 1:465).
- *Clinical sensitivity* of *BRCA1* and *BRCA2* mutations and breast cancer by age 70: 1.5% (reasonable range: 1.0% to 2.0%).
- *Penetrance* of the two mutations by age 70: 55% (reasonable range: 35% to 65%).

Other important findings of the ACCE review for family health history and *BRCA1* and *BRCA2* mutation testing include the following:

- Some common sources for information about mutation testing and breast cancer provide information that is not consistent with the current literature.
- The current protocols for interpreting family histories for breast and ovarian cancers are not strictly evidence-based; they do not agree on what constitutes evidence of an inherited form of breast/ovarian cancer (7) and are likely to identify some women as screening positive whose probability of having a mutation is relatively low (8).
- Significant gaps in knowledge exist for estimating the analytic validity and clinical validity of *BRCA1* and *BRCA2* mutation testing. The reason for these gaps in knowledge is mainly due to the expense of full sequencing and the limitations imposed on both genes by the patents held by Myriad Genetic Laboratories, Inc.*

** Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.*

Programs that provide information to health professionals or patients about the epidemiology of breast cancer and *BRCA1* and *BRCA2* mutation testing might consider reviewing their materials in order to determine whether updates are warranted. In addition, any group considering implementing a family health history screening protocol in the general population (e.g., in primary care) should carefully evaluate the performance of the screening protocol prior to its widespread introduction. *For more information on Family History, see Chapter 2, CDC's Family History Public Health Initiative: 2005 Update.*

Preconception and Prenatal Screening for Cystic Fibrosis via *CFTR* Carrier Testing

During 1997, a National Institutes of Health consensus conference recommended offering cystic fibrosis transmembrane conductance regulator (*CFTR*) carrier testing to pregnant couples and couples planning to become pregnant (9). Soon after this recommendation was made, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG) were charged with overseeing the implementation of *CFTR* carrier testing. They produced recommendations that include the panel of mutations to be tested and patient educational materials (10,11). A full ACCE review was performed after these policies were introduced in 2001. For more information, visit the website: *http://www.cdc.gov/genomics/activities/ogdp/2003/chap09.htm*.

Results of the ACCE review were used by ACMG to update Laboratory Standards and Guidelines in 2004 (12). Selected new or important findings from the ACCE review include the following:

- Previously unpublished evidence showed for the first time that *CFTR* mutation testing is highly reliable. Analytic sensitivity (i.e., the proportion of samples with a *CFTR* mutation that was correctly identified) was approximately 98%, whereas analytic specificity (i.e., the proportion of samples without a correctly identified *CFTR* mutation) was approximately 99.7% (13).

- Clinical sensitivity (i.e., the proportion of carrier couples that could be identified by the ACMG-recommended panel of mutations) was estimated for broad racial/ethnic categories (e.g., 78% of non-Hispanic Caucasian carrier couples, 42% of African American carrier couples).

- The prevalence of "classic" cystic fibrosis (CF) was estimated for the same racial/ethnic categories (e.g., 1:2,500 for non-Hispanic Caucasian couples, 1:15,100 for African American couples).

- Methods and data are lacking to evaluate the impact of preconception and prenatal screening for CF. Current regulations (e.g., Health Insurance Portability and Accountability Act of 1996, or HIPAA) and health care reimbursement issues complicate the collection of key information (e.g., specific risks and benefits, acceptability, and cost-effectiveness) (14).

Health care providers interpreting *CFTR* mutation test results as part of preconception or prenatal carrier screening for CF should review the revised laboratory standards and guidelines for updated information. The ACCE review helps to clarify issues related to the offering of this testing to members of different racial/ethnic groups. Because of the low prevalence and poor clinical sensitivity of some of these group populations, the resources required to detect each carrier could be more than 40 times greater than in other racial/ethnic groups.

Lessons Learned

The ACCE project has provided the following lessons:

- Comprehensive evidence-based reports, such as an ACCE review, are expensive, are labor intensive, and require multiple areas of expertise. Final reports are often cumbersome to review and digest. These reviews, therefore, are best undertaken by a group that has experience in extracting and summarizing data from the literature with guidance from content experts.

- Overall, the benefit of a structured, systematic approach to evidence collection and evaluation for any given topic must be balanced against the urgency of need for such an investment of time and effort. At present, only a limited number of genetic tests are likely to have sufficiently broad applications and available data to justify such an effort. The ACCE process was designed specifically to produce an evidence base for policy decisions while refraining from making recommendations.

These and other issues concerning evidence-based reviews of genetic testing are being addressed by a new CDC initiative entitled Evaluation of Genomic Applications in Practice and Prevention (EGAPP). *For more information on this initiative, see Chapter 6, Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach.*

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Chapter 6

Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach

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What Is the EGAPP Project?

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project is a 3-year model project developed by the Centers for Disease Control and Prevention's (CDC's) Office of Genomics and Disease Prevention (OGDP). The goal of this initiative is to support the first phases of a coordinated process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States. The EGAPP Project aims to draw on existing recommendations for action in the United States (1,2) as well as from knowledge gained from previous CDC initiatives, including the recently completed ACCE Project (3,4). This project will also integrate knowledge from existing processes for evaluation and appraisal (e.g., Agency for Healthcare Research and Quality/U.S. Preventive Services Task Force [*www.ahrq.gov/clinic/uspstfab.htm*], and the CDC Task Force on Community Preventive Services [*www.thecommunityguide.org/about/default.htm*]).

The ACCE Project

Conducted by the Foundation for Blood Research under a cooperative agreement with CDC's Office of Genomics and Disease Prevention (OGDP), the ACCE project proposed and tested a model process for collecting, evaluating, interpreting, and reporting data about DNA and related testing for disorders with a genetic component (*http://www.cdc.gov/genomics/activities/fbr.htm*). An important aspect of this process was the identification of gaps in knowledge.

ACCE takes its name from the four previously defined components of evaluation: **A**nalytic validity; **C**linical validity; **C**linical utility; and **E**thical, legal, and social implications (1,2). The evaluation process is based on an analytic framework of more than 40 targeted questions that establish the specific clinical disorder being evaluated, the test(s) to be used, and the setting in which the testing will be conducted (e.g., primary iron overload in adults using HFE testing in the setting of population screening).

For more information on the ACCE Project, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2 and CFTR.

Why Is Evaluation of Emerging Genomic Applications a Public Health Issue?

The success of the Human Genome Project has led to increasingly rapid translation of genomic information into clinical applications. Genetic tests have been developed for approximately 1,100 diseases, and more than 800 disorders are currently available for clinical testing (5). Although most genetic testing is used for diagnosing rare genetic disorders, a growing number of genetic tests have population-based applications, including carrier identification, predictive testing for inherited risk for common diseases, and pharmacogenetic testing for variation in drug response. These tests and other anticipated applications of genomic technologies for use in screening and prevention have the potential for broad public health impact.

Consumers, health professionals and government advisory groups have raised issues about the current status of genetic-testing implementation and oversight, including the need to develop evidence to establish efficacy and cost-effectiveness before tests are commercialized (1,2,6-8). In addition, as consumers' interest in and demand for new genomic technologies continues to rise, the need for timely and reliable information becomes increasingly crucial. This information will enable health care providers, payers (insurers), consumers, and policy makers to decide which tests are safe and effective and to ensure that they are used appropriately. Expert panels, professional organizations, and clinical experts (e.g., Task Force on Genetic Testing, Secretary's Advisory Committee on Genetic Testing) have produced recommendations on the development of genetic tests (1,2,6-8). However, a coordinated approach has not yet been developed for effective translation of genomic implications into clinical practice and health policy and for post market monitoring.

EGAPP Working Group

The EGAPP Project has established an independent, non-federal Working Group (*www.cdc.gov/genomics/gtesting/egapp.htm#wgroup*) composed of experts from fields including health care, epidemiology, genomics, public health, laboratory practice, and evidence-based medicine. Key roles of the working group include:

- Consider input from stakeholders and experts, develop criteria, and prioritize and select topics for evidence-based review.
- Establish methods and process for evidence reviews.
- Oversee expert and peer review of commissioned evidence reports.
- Develop conclusions or recommendations based on the evidence.

- Provide advice about other project activities, such as pilot data collection studies and project evaluation.

Stakeholders

A key objective is to identify, engage, and continuously involve a wide range of stakeholders in the project. Early participation of stakeholders is needed to:

- Suggest priority topics for review.
- Provide input on the content and format of information that is needed and useful from the stakeholders' different perspectives.
- Contribute technical expertise.

In later stages of the project, stakeholder groups will have an important role in developing informational messages targeting specific audiences, based on the evidence reviews and the Working Group's conclusions/recommendations. For this model project, the primary target audiences are health care providers and consumers, and the key secondary audiences are policy makers and health care purchasers and payers. The stakeholder groups will also provide important feedback on the value and impact of the evidence reports and informational messages developed.

Other EGAPP Activities

In addition to establishing the EGAPP Working Group and involving stakeholders, project activities will include:

- Supporting evidence-based reviews performed by expert groups on topics selected by the Working Group.
- Supporting pilot data collection studies to provide needed data on issues such as utilization, access, performance in practice, or the resolution of specific identified gaps in knowledge.
- Implementing a comprehensive plan for evaluating the EGAPP Project.
- Considering mechanisms to sustain an ongoing systematic process for evaluation of genomic applications.

This project will focus on tests that have the potential for broad application and public health impact (e.g., population screening, tests for guiding clinical intervention). The large number of genetic tests used for diagnosing rare, single-gene disorders are less likely to be reviewed; however, the methods and standards

developed for EGAPP reviews may be of interest to groups focused on improving access to quality genetic tests for rare disorders. *For more information on this topic, see Chapter 8, Enhancing Genetic Testing for Rare Diseases: Improving Availability, Access, and Quality.*

Expert Meeting on Evidence-Based Review of Genomic Applications

On January 24-25, 2005, CDC hosted an invitational conference that brought together 21 experts in the areas of evidence-based medicine, health care, genomics, health technology assessment, epidemiology, ethics, and health economics from the United States, Canada, and the United Kingdom. Participants also represented various professional settings, including public health, academia, government agencies, the U.S. Preventive Services Task Force and the Community Preventive Services Task Force, clinical and laboratory practice, industry, and regulation. The participants considered both existing and potential approaches and methodologies for systematic evaluation of genetic tests and other genomic applications as well as reviewed lessons learned by existing programs and projects that conduct systematic reviews.

Why Might EGAPP Project Activities Interest State and Local Public Health Professionals?

The EGAPP Project plans to engage state and local public health professionals and involve them in the evaluation process. For example, these important stakeholders can help to identify emerging genetic tests and technologies for which accurate and objective data are most acutely needed in order to inform appropriate use and policy development. The stakeholders may also contribute to other proposed activities, such as design and dissemination of information summaries to target audiences, pilot studies to collect data on test utilization and performance in practice, and efforts to develop public-private partnerships.

How Will Success Be Measured?

Comprehensive evaluation of the process, products, and impact is fundamental to this model project. Outcomes of interest include the ability to establish and support a transparent and publicly accountable process for systematic evaluation, engage stakeholders, and develop and maintain effective partnerships and collaborations. This project will also seek feedback on the quality and usefulness of products, such as evidence reports and summaries; working group conclusions/recommendations; targeted informational messages; and post-market data on quality, acceptability, or utilization of tests. Impact will be assessed through feedback from the stakeholders on project awareness, use and value of information, success of dissemination, and measurable changes in practice, policy, or reimbursement/coverage decisions.

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Chapter 7
Newborn Screening for Cystic Fibrosis: A Public Health Response

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What Is Cystic Fibrosis?

Autosomal recessive
Condition manifested only when a gene variant is inherited from each parent.

Cystic fibrosis (CF) is an **autosomal recessive** genetic disorder that affects approximately 1/3,700 births in the United States (1). People with CF have mutations in both copies of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7. Although more than 1,000 mutations of the *CFTR* gene have been identified, 1 mutation, Δ*F508*, accounts for two-thirds of all *CFTR* mutations worldwide (2,3). CF disrupts the normal functioning of multiple organ systems and can affect the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract (2). In 2001, the median predicted average age of survival in persons with CF was 33 years (4).

Why Test Newborns for Cystic Fibrosis?

Early diagnosis of CF by newborn screening can help avoid unnecessary physician visits, hospitalizations, and diagnostic tests, along with the costs and parental anxiety associated with having an ill but undiagnosed newborn, and allow for the early introduction of therapies that have proven to be beneficial (5). The median age at which CF is clinically diagnosed based on signs and symptoms (excluding **meconium ileus**) is 14.5 months, compared with 0.5 months for infants diagnosed by newborn screening (6). Naturally, however, the benefits of newborn screening for CF must be balanced with costs and risks, including those associated with false positive test results.

Meconium ileus
An intestinal obstruction present at birth due to abnormally thick meconium that blocks the passage of stool out of the ileum and into the colon.

Newborn screening is not the only option for early detection of CF. Professional organizations have endorsed the use of prenatal carrier screening (7); however, preliminary data suggest that ≤20% of pregnant women in the United States receive this type of screening (8). In addition, compared with a 95%-99% sensitivity for newborn CF screening (5), the sensitivity of prenatal screening is ≤78% for the non-Hispanic white population and lower for other racial and ethnic groups (9). *For more information, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2 and CFTR.*

Public Health Response

In November 2003, the Centers for Disease Control and Prevention (CDC), along with the Cystic Fibrosis Foundation (CFF), held a workshop to address newborn screening for CF. The three objectives of the workshop were to:

- Review and evaluate the scientific evidence on benefits and risks of newborn screening for CF.
- Review screening, diagnostics, and follow-up concerns in CF newborn screening decision-making.
- Disseminate information about models and best practices for states that choose to adopt newborn screening for CF.

A review of the benefits, harms, and recommendations for implementing newborn screening for CF was published October 15, 2004, in the MMWR Recommendations and Reports, and is summarized in the following text box (5).

Recommendations

The magnitude of the health benefits from screening for CF is sufficient that states should consider including routine newborn screening for CF in conjunction with systems to ensure access to high-quality care.

- In reaching a decision as to whether to add newborn screening for CF, states should consider available state resources and priorities as well as available national guidelines regarding CF screening, diagnosis, and treatment.
- States that implement newborn screening for CF should collect follow-up data in collaboration with CF care centers and analyze this information to monitor and improve the quality of CF newborn screening. In particular, states should collect, share, and analyze data by using standard protocols to evaluate and optimize laboratory algorithms used to screen for CF and refer for diagnosis. States seeking guidance on optimal laboratory protocols might wish to consult with states having more experience in conducting CF screening of newborns.
- Newborn screening for CF should be accompanied by rigorous infection control practices to minimize the risk to children with CF detected at an early age of acquiring infectious organisms associated with lung disease from older patients. Further research is needed to evaluate and optimize these practices.

- Newborn screening systems should ensure parental and provider education and communication of screening results to primary-care providers in a manner that will ensure prompt referral to diagnostic centers. For CF, these should be centers skilled in providing both sweat tests to young, presymptomatic children with CF and accurate and effective counseling to families, including those with infants identified as carriers. States are recommended to work with each other and with professional organizations and federal agencies to develop approaches to provide newborn screening information to parents during the prenatal and perinatal periods on all conditions, including CF, to facilitate informed choices and appropriate responses to positive screen results.

In addition, a recent editorial published in the journal American Family Physician provided a brief overview of the main findings and recommendations from the MMWR report (10).

Weighing the Costs and Benefits for Universal Newborn Screening for CF

CF may not fulfill the traditional criteria used to justify universal newborn screening, including the specification that immediate intervention should be available to prevent devastating outcomes. Infants with CF rarely die during the newborn period and do not suffer severe intellectual disability due to a lack of early intervention; however, there is evidence of moderate clinical benefit from early detection of CF. Alternative criteria balancing the benefits and risks of screening need to be considered for disorders such as CF; furthermore, the complex policy decision of whether to adopt screening also requires consideration of costs, resources, and priorities (5).

Two randomized, controlled trials and additional observational studies of newborn screening for CF have reported benefits in terms of improved growth, cognitive outcomes, reduced hospitalizations, and increased survival for subjects diagnosed through CF newborn screening. Evidence of any pulmonary benefit remains uncertain, however, and data are lacking for evaluating effects on health-related quality of life. In addition to the health benefits for children, newborn screening provides potential familial benefits by eliminating the "diagnostic odyssey" that generally precedes clinical diagnosis (e.g., multiple doctor visits, unnecessary tests and hospitalizations, considerable healthcare costs, parental anxiety) (5).

The benefits of newborn screening, however, must be weighed against the risks, including the early acquisition of P. aeruginosa infection by infants exposed in CF

clinics to older children with CF who have active lung infections. Strict infection control practices and separation of asymptomatic infants and children from patients with established disease can reduce early acquisition of P. aeruginosa and other lung infections (11). Careful implementation of state newborn screening programs could limit the number of false-positive results and help facilitate the communication of genetic results to parents to minimize parental anxiety and misunderstanding.

Although no complete cost-effectiveness analysis has been published for newborn CF screening, partial cost data from Wisconsin suggest that screening costs were largely offset by savings from reduced demand for sweat tests and that laboratory screening cost for CF is comparable to other newborn screening tests that are in common use (12).

Adding CF Screening to Existing Newborn Screening Programs

Professional organizations, including the American College of Medical Genetics (ACMG) (13), the March of Dimes (14), and CFF (15) have recommended that states screen for CF based on the benefits of early diagnosis. As of the end of 2004, the following 10 states had implemented universal newborn screening for CF: Colorado, Florida, Massachusetts, Mississippi, Montana, New Jersey, New York, Oklahoma, South Carolina, Wisconsin, Wyoming. In addition, certain hospitals in three other states collect specimens at hospital discharge for screening by a state public health laboratory (Montana), academic laboratories (Connecticut), or a commercial laboratory (Pennsylvania) (16). Other states are considering adding CF to their existing screening programs.

Challenges in Implementing CF Screening

The addition of a new test to a newborn screening panel presents many challenges. CF screening programs are complex and should be developed in a deliberate fashion, with attention to the experience of existing programs. For states considering CF newborn screening, these challenges include the following:

- Establish appropriate laboratory protocols and algorithms.
- Implement proper and timely follow-up and facilitate communication of genetic information to parents.

Analytic validity
The ability of a test to accurately and reliably measure a specific analyte or identify a mutation of interest.

Clinical validity
The ability of a test to accurately and reliably identify individuals who either have or will have the disorder or phenotype of interest.

Laboratory Implementation Issues

Laboratory implementation for CF screening should consider the testing algorithms to be used, the **analytic validity** and **clinical validity** of the testing, and the laboratory (state, private, or academic) that will perform the testing.

Plasma concentrations of immunoreactive trypsinogen (IRT) are elevated at birth in CF-affected infants and can be easily detected in dried blood spots. When used in conjunction with IRT screening, commercial tests for the most common mutations of the *CFTR* gene can detect most infants with CF (17,18). Screening protocols begin with an initial IRT test conducted on the newborn blood spot specimen collected within 48 hours of birth. In the IRT/IRT protocol, newborns with an elevated IRT in the first test are tested again at approximately 2 weeks of age. If IRT is still elevated, the infant is referred for a sweat test. In other protocols, the second tier test is mutation detection by DNA analysis of the original specimen. States have elected to use either IRT/IRT or IRT/DNA screening protocols. In many newborn screening programs, IRT testing can be added easily, because the technology needed to conduct IRT testing is already in place. Adding DNA testing, however, may require additional equipment and expertise. Some programs may choose to implement all CF screening components within their own laboratories, whereas other programs may choose to partner with academic or private laboratories for some or all of their testing.

To help monitor the analytic validity of CF newborn screening tests, CDC's Newborn Screening Quality Assurance Program has operated a proficiency testing (PT) program for IRT since 2002. During 2003, the program was expanded to add DNA testing for the Δ*F508* mutation. Each quarter, a panel containing positive and negative specimens is distributed to 59 laboratories in 15 countries. CDC is working to develop specimens that can be used with all molecular methods. Newborn screening programs estimate clinical validity by tracking diagnostic outcomes of infants with positive screening results and monitoring the number of missed cases.

Follow-up and Communication Issues

Protocols and resources for adequate follow-up are essential for children who screen positive for CF. States should ensure that these children are referred in a timely manner to a diagnostic CF care center for sweat testing and genetic counseling. Identifying **carriers** is an unavoidable result of CF newborn screening using IRT/DNA protocols and requires genetic counseling resources for families. Providing more information to parents during both the prenatal and perinatal periods can help state programs alleviate parental anxiety and misunderstanding of CF screening results.

Carrier
A person who has just one copy of a recessive disease-causing gene variant and does not have the disease in question.

Conclusion

Newborn screening for CF represents one model for decision making in the public health application of genetic-testing strategies. A decision to adopt population-based screening should be preceded by large-scale pilot studies of screening to

address questions of implementation and to assess impacts, including potential risks. Other programs can apply the lessons learned from these pilot studies in order to ensure that "more good than harm" results from newborn screening for CF (19).

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Chapter 8

Enhancing Genetic Testing for Rare Diseases: Improving Availability, Access, and Quality

W. Andrew Faucett, D. Joe Boone, and Bin Chen

Genetic Testing for Rare Diseases

Although rare diseases and disorders are uncommon individually, they collectively affect a significant portion of the population. The majority of the 6,000–7,000 health conditions that at present are generally considered rare diseases are recognized as genetic conditions (1), making genetic testing an essential element in disease diagnosis and management. Rare diseases represent a major frontier in the development of genetic tests. Information from GeneTests (*www.genetests.org*), a publicly-funded information resource on genetic testing and its use in clinical practice, indicates that during a recent 10-month period, from May 2004 through March 2005, new genetic tests were introduced into clinical settings for more than 100 diseases, of which the majority were rare (2). Moreover, most newborn conditions found through screening are rare genetic diseases. With the current expansion of newborn screening programs, availability of and access to quality diagnostic genetic testing following screening has become a growing public health issue. *For more information on this topic, see Chapter 7, Newborn Screening for Cystic Fibrosis: A Public Health Response.*

Currently, the use of genetic testing is limited to only a small number of approved clinical laboratories and is available for only a small percentage of rare diseases. For many rare conditions, genetic testing may be available at only one or two laboratories in the United States, or even possibly worldwide, or at laboratories that primarily conduct research studies. As of March 2005, the GeneTests website (*www.genetests.org*) reported that clinical testing was available for 801 diseases, whereas testing for another 315 diseases was available only in research settings (2). Although GeneTests emphasizes information on DNA-based genetic tests, a huge gap exists in the availability of quality genetic testing—including molecular, biochemical, and other genetic tests—for rare diseases.

Genetic research is progressing rapidly, with an average of 60–100 new gene findings added each month to the Online Mendelian Inheritance in Man (OMIM) database (3). The total number of rare diseases is increasing as well, with approximately 20 additional rare diseases reported monthly in the scientific

literature (4). A limited survey of GeneTests conducted from August 2003 to April 2004, however, revealed that fewer than 10 new genetic tests per month had been added to the database (5), indicating a growing gap between our understanding of the genetic basis of diseases and the availability of quality clinical laboratory testing. This disparity is further aggravated, by the current lack of an established process to move potential tests for rare diseases from the research phase to a clinical laboratory setting. *For more information on this topic, see Chapter 6, Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach.*

What Is a Rare Disease?

There is no uniform definition of a rare disease, although most definitions overlap. This report is not restricted to one single definition. Some examples of applicable definitions and their sources are as follows:

- A "rare disease or condition'' means any disease or condition which affects less than 200,000 persons in the United States. — The Orphan Drug Act (6).
- A rare or "orphan" disease affects fewer than 200,000 people in the United States. — National Organization of Rare Disorders (NORD) website (7).
- A rare disease (also called an orphan disease) is a disease or condition affecting fewer than 200,000 persons in the United States. An estimated 25 million people in the United States have a rare disease. — Office of Rare Diseases, National Institutes of Health (1).
- Diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year.— 21 CFR 814 Premarket Approval Of Medical Devices; Subpart H: Humanitarian Use Devices (8).
- In Europe, a disease is considered as rare when it affects 1 person per 2,000 — Orphanet (4).

For many genetic conditions, the actual number of people with the condition is not well documented and prevalence must be estimated. Genetic researchers generally agree that most single-gene genetic conditions should be considered rare diseases, which currently comprise an estimated 6,000–7,000 diseases that together affect 25 million, or approximately 1 in 12 people in the United States.

Public Health Implications of Improving the Translation of Rare Disease Genetic Testing

In 2004, the Centers for Disease Control and Prevention (CDC) and other interested groups began to discuss how to improve the availability and quality of diagnostic rare disease testing and how public health could move the process forward. The goals were to:

- Assure access to quality laboratory testing.
- Promote translation of research into practice.
- Facilitate test development, validation, and implementation.
- Identify opportunities and barriers.
- Enhance information collection and synthesis.
- Promote collaboration, cooperation, partnership, and community involvement.

Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing

In May 2004, the conference "Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing" (9) was held in Atlanta, Georgia, as a collaborative effort of CDC, Emory University School of Medicine, the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH), the American Society for Human Genetics (ASHG), the American College of Medical Genetics (ACMG), the Health Resources and Services Administration (HRSA), and the Genetic Alliance. Conference participants included more than 50 experts from government, academic institutions, professional organizations, laboratories, industry, health care payers, and patient advocacy groups. The main goals of the conference included:

- Review of the current rare disease testing landscape.
- Discussion of the problems and concerns regarding the quality, availability, access, and resources for rare disease testing.
- Identification of needs and barriers to quality testing.
- Exploration of potential approaches to promoting quality testing.

- Development of specific recommendations and action items for improving availability of and access to quality laboratory testing for rare diseases.

The conference included plenary presentations on:

- Analyses of currently available genetic testing for rare diseases and recent trends.
- **CLIA** oversight of clinical laboratories.
- Roles of federal and institutional bodies in assuring safety and protection of human research subjects.
- Implications of the HIPAA Privacy Rule (10) for clinical research.
- Current working approaches that provide quality rare disease testing.
- Current strategies that facilitate translation of potential tests into practice.
- Past and current efforts to improve quality, availability, and access for rare disease genetic testing.

CLIA (Clinical Laboratory Improvement Amendments)
CLIA, 42 CFR Part 493, sets forth federal standards for laboratories performing patient testing to ensure the quality of laboratory testing in the United States.

Public Health Actions: Improving the Translation of Tests for Rare Diseases from Research to Clinical Practice

All attendees agreed upon the following goals and actions by the conclusion of the meeting:

- Provide education to promote quality translation of research findings into clinical testing for rare diseases and to advance understanding of quality standards for patient testing. Appropriate strategies and teaching materials should be developed for the research community, institutional review boards (IRBs), providers and users of laboratory services, health care payers, patients, research participants, and advocacy groups in order to minimize adverse impact on access to testing.
- Develop guidance, strategies, and criteria for evaluating the clinical readiness of potential tests. Issues needing further exploration include how recently developed rare disease tests should be validated and how analytic validity, clinical validity, and clinical utility should be established for these tests. *For more information on this topic, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2 and CFTR.*

- Develop reasonable and achievable **quality assurance** strategies for clinical genetic testing for rare diseases.

- Establish mechanisms and strategies to promote quality data collection during each step of test development through clinical application.

- Establish partnerships and networks to improve and facilitate research translation, data sharing, clinical availability, and quality assurance.

- Enhance infrastructure to provide momentum and enable development of activities needed, including facilitating the translation process, assuring the quality of testing services, and improving access to testing.

Quality assurance (QA)
QA includes all actions taken to ensure that laboratory standards and protocols are adhered to, and that test results consistently meet performance requirements.

Public Health Actions: Ensuring Access and Quality of Rare Disease Testing

The conference concluded with the following immediate outcomes and next steps:

- Agreement was made to form the North American National Laboratory Network for Rare Disease Genetic Testing with six reference laboratories (11).

- The American Society of Human Genetics and other professional organizations agreed to organize educational activities and develop guidance for rare disease genetic testing.

- The Office for Human Research Protections (OHRP) confirmed its commitment to providing education to IRBs regarding their role in safeguarding the release of individual test results in clinical research (12).

- Agreement was made to hold a follow-up "Integration Conference" in 2005 to convert the recommendations into projects and action items and to develop additional recommendations.

To accomplish these goals, public health professionals will need to develop an infrastructure for guiding the process that would include strategies for determining how best to translate rare disease tests from research to clinical testing; how to ensure that access is not lost as the quality of testing is emphasized; and how to decide which tests public health efforts should focus on first.

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Chapter 9

Centers for Genomics and Public Health: An Update

Introduction

During 2001, the Centers for Disease Control and Prevention (CDC), in collaboration with the Association of Schools of Public Health (ASPH), established the first Centers for Genomics and Public Health. These Centers—located at the University of Michigan, the University of North Carolina, and the University of Washington—each quickly became a hub of expertise that built on and complemented existing university programs as well as created new links with local and state health departments. Today, the Centers are recognized national resources for public health genomics that contribute to the knowledge base, provide technical assistance to local, state, and regional public health organizations, and develop and deliver training to the public health workforce.

In initiating this collaborative approach with ASPH, CDC hoped to identify gaps in public health research and to demonstrate, through the use of real examples, the translation of gene discoveries into disease prevention and improved health. This chapter presents an overview of the progress made by the Centers in reaching their goals and objectives over the past four years.

University of Michigan Center for Genomics and Public Health

(*www.sph.umich.edu/genomics/*)

Michigan Center Mission Statement

The Michigan Center for Genomics and Public Health (MCGPH) seeks to integrate genomic discoveries into public health practice, with consideration of the ethical, legal, and social issues associated with the application of these discoveries as well as the involvement of the community at large.

MCGPH projects have included:

- Online Genomics Training: Six Weeks to Genomic Awareness.
- Distance Learning Course: Issues in Public Health Genetics.
- Literature Review: Genetics of Long QT Syndrome.

Online Genomics Training: Six Weeks to Genomic Awareness
Six Weeks to Genomic Awareness is an in-depth, online training series on public health genomics that developed from the collaborative relationship between the MCGPH and the Michigan Department of Community Health (MDCH). The series was designed to provide an understanding of the role of genomics in public health and to reflect the themes most relevant to public health workers, including basic information about molecular genetics, gene-environment interactions, gene-disease associations, genes in populations, genetic testing, genetic resources, and ethical, legal and social (ELSI) implications.

Distance Learning Course: Issues in Public Health Genetics
Issues in Public Health Genetics is a mentored, distance learning, for-credit course that, beginning in January 2005, has been offered to students and public health professionals as a free pilot class and is accessed through Internet broadcasts and CD-ROMs. The course focuses on ethical, legal, and social issues arising from the increasing use of genetic technologies in medicine and public health. In the future, this class will be offered for a fee as part of the regular university curriculum.

Literature Review: Genetics of Long QT Syndrome
Cardiac arrhythmia that causes sudden death is most commonly the result of coronary heart disease. Genetic causes of arrhythmia, however, such as long QT syndrome (LQTS), which affects cardiac ion channels, are increasingly being recognized as having public health consequences. In the United States alone, LQTS is responsible for an estimated 3,000 deaths per year (1). Some arrhythmia susceptibility-conferring genetic polymorphisms have frequencies of 25% or higher in subpopulations in the United States and abroad (2,3).

Channelopathy
Alterations that disturb the formation and function of channels at the cell surface that convey potassium, sodium, calcium, and other ions. Cardiac ion channelopathies can lead to potentially fatal arrhythmias (heart attacks).

Phenotype
The observable properties conferred by one's genetic makeup (contrast with genotype, which is the specific genetic constitution of an individual).

Faculty members at the MCGPH and University of Michigan School of Medicine have reviewed the literature on the long QT syndrome family of cardiac **channelopathies** for the time period 1975-2004. A report entitled The Long QT Syndrome Family of Cardiac Ion Channelopathies (by Stephen M. Modell, MD, MS, and Michael H. Lehmann, MD) has been submitted for publication. This report summarizes published case reports and population-based studies from 20+ countries, as well as research emerging from the International LQTS Registry. Review of the most prevalent and illustrative LQTS mutations and polymorphisms described in this report shows that particular coding regions are structurally more prone to mutations than others and that **phenotypic** severity can depend on mutation site. Gene-gene interactions, in cases where a disease conferring mutation coexists with an LQTS polymorphism, can influence phenotype. Some 10%-15% of LQTS genetic variants are susceptible to triggering by drugs and metabolic disturbances (4). Race-ethnicity and gender can show differential mutation and disease associations, but LQTS is not limited to any one group of people. The report includes family-based and population-screening methodologies

that optimize sensitivity and cost-effectiveness. Breaking developments, such as the commercialization of genetic testing for long QT syndrome, are also covered.

University of North Carolina Center for Genomics and Public Health

(*http://www.sph.unc.edu/nccgph/*)

North Carolina Center Mission Statement

The mission of the North Carolina Center for Genomics and Public Health (NCCGPH) is to foster understanding of the role of genomic information in public health programs and policies for the improvement of human health. This Center focuses on adult onset chronic disease, with an emphasis on cancer.

NCCGPH projects include:

- Breast Cancer Family History Training Module.
- Comprehensive Cancer Control Plan Review for Genomics Components.
- Evaluation of Quality in Promotional Material for Genetic Tests.

Genomic Awareness Campaign

The NCCGPH conducted a needs assessment to evaluate attitudes of public health workers in North Carolina regarding genomics issues. Key informant interviews and focus groups demonstrated that the level of awareness regarding genomics was low and that there was a strong interest in further training in this area. In direct response to the needs assessment, and in response to a request from the North Carolina Division of Public Health, NCCGPH developed a Genomic Awareness Campaign (GAC). The GAC consisted of online training materials and in-person presentations that were made available to personnel in local health departments. The training materials include basic definitions of genomics and genetics, the relationship between genomics and public health, case studies, and questions for discussion. NCCGPH created the GAC with the involvement and advice of senior staff in the NC Division of Public Health to best tailor the content and presentation style to personnel in local health departments.

NCCGPH has conducted the GAC presentation at two annual meetings of the North Carolina Association of Public Health Nurse Administrators and at the annual meeting of the NC Dietetics Association, which is attended by registered dieticians in public health and private practice. It has also been presented to local public health departments throughout the state. GAC training and other materials can be viewed at the NCCGPH website under "Tools" (*www.sph.unc.edu/nccgph/tools/index.htm*).

Breast Cancer Family History Training Module
One familiar genomic tool that is currently accepted and applied in nursing practice is the collection of a family history. Although public health nurses are trained to obtain a family history from each of their patients, the information is not comprehensive enough to identify potential genetic conditions (5). The NCCGPH developed a Breast Cancer Family History Training Module for public health nurses through a formative evaluation process. This training module includes basic definitions of inheritance patterns; how to draw and interpret a pedigree; and how to classify women as low, medium and high-risk for breast cancer based on their family history and personal risk factor profile. Several case studies are included. The module incorporates "lessons learned" from nurses in public health practice; these lessons include recommendations that educational material should build upon existing knowledge, feature case studies, and be presented in a form that is comprehensible to persons with varying scientific backgrounds. The module combines established training principles from both the nursing and health education literature. The module is available for distribution, although it is not available online. For more information, contact NCCGPH.

Comprehensive Cancer Control Plan Review for Genomics Components
The CDC identified state Comprehensive Cancer Control (CCC) plans that mentioned genomics or genetics, and NCCGPH reviewed these **cancer control plans** in detail. The assessment included a review of CCC plan content as well as successes and barriers for implementation of genomics-related cancer control initiatives. The project was conducted in two phases: a content analysis of 30 written state CCC plans for genomics components, followed by telephone interviews with CCC plan coordinators in the 16 states that had CCC plans with genomics components.

Cancer control plans
Comprehensive documents produced by state health departments to address screening, treatment and prevention of cancer.

Most states emphasized raising awareness and educating health care providers and the public about the role of genomics in cancer control. Many states considered awareness of family history to be an important aspect of their CCC plans. Approximately two-thirds of states with family history components in their plans had already begun to implement them. Adequate funding and productive partnerships improved the likelihood of implementation success. Virtually all of the state CCC coordinators reported that they would benefit from additional training in cancer genetics and public health genomics such as cancer control plans (6).

Evaluation of Quality in Promotional Material for Genetic Tests
Many commercial genetic tests are now available to the public. Some of these tests are designed to identify genes or gene products that are present with increased frequency in people with certain types of illness, disease, or other health conditions. Other genetic tests and products have more social or legal

applications, such as ancestry profiling, biological relationship testing, and DNA banking. The NCCGPH is currently conducting a comprehensive and systematic evaluation of promotional material for genetic tests and products that are accessible to consumers on the World Wide Web. Topics of interest include persuasive tactics used in promotional materials, quality and accuracy of information presented, and characteristics of target audiences. The project will be completed during 2006, after which the results will be published. A PowerPoint presentation of this project is available at *www.sph.unc.edu/nccgph*. *For more information on this topic, see Chapter 4, Direct-to-Consumer Marketing Campaign: Evaluation of Quality in Promotional Material for Genetic Tests for Susceptibility to Breast and Ovarian Cancer.*

University of Washington Center for Genomics and Public Health

(*http://depts.washington.edu/cgph/*)

University of Washington Center Mission Statement

The University of Washington Center for Genomics and Public Health (UWCGPH) seeks to integrate advances in genetic technology into public health practice and offer research and educational opportunities for public health students and professionals.

UWCGPH projects include:

- Knowledge Base Development: Human Genome Epidemiology (HuGE) Reviews.
- Training: Teleconference on the Genomics of Obesity.
- Technical Assistance:
  1. Genomics Survey Coordination Workgroup
  2. Interactive Brown Bag on Public Health Genomics.

Knowledge Base Development: Human Genome Epidemiology (HuGE) Reviews

Faculty and students at the UWCGPH performed an in-depth review of the genetic and epidemiological literature on familial hypercholesterolemia (FH). The genetics of this disease have been extensively studied since the 1930s. Characteristics of FH include elevated cholesterol levels, **xanthomata**, and a family history of premature heart disease. The clinical FH phenotype results from mutations in the low-density lipoprotein receptor gene (*LDLR*) and the apolipoprotein-B 100 gene (*APOB*). Because of the breadth of the subject material, the review was separated into three papers, all of which were published in the American Journal of Epidemiology and are available on the HuGE website (7-9).

Xanthomata
Localized collections of cells containing lipid material, including cholesterol and triglycerides.

- The Prevalence Review describes current diagnostic tools for FH, catalogues prevalence studies of *LDLR* and *APOB* mutations in FH subjects, and assesses FH screening programs (7).

- The Association Review evaluates association studies of clinical FH, as well as specific mutations in *LDLR* and *APOB*, with coronary heart disease (8).

- The Mini-Review summarizes studies of FH as a potential risk factor for peripheral vascular and ischemic cerebrovascular disease (9).

These reviews identified several areas for future research, including:

- Examining the role of gene-environment interactions in FH.

- Assessing the strength of the association between incident **ischemic stroke** events and FH.

- Evaluating the public health impact of genetic FH screening programs.

Ischemic stroke
Ischemic stroke is caused by blockage in an artery that supplies blood to the brain, resulting in a deficiency in blood flow (ischemia).

Training: Teleconference on the Genomics of Obesity
In collaboration with the Chronic Disease Program directors and the CDC Division of Nutrition and Physical Activity, the director of the UWCGPH, Karen L. Edwards, PhD, presented an October 2004 teleconference on Obesity: Current Topics in Genetics. Objectives for participants were to:

- Be familiar with the evidence for genetic influences on obesity.

- Understand how genetic factors can influence obesity, both directly and indirectly.

- Be familiar with one current application of genomic information for public health practice.

Materials from the teleconference, including an audio-assisted slide presentation and an informational brochure, are available on the UWCGPH website (*http://depts.washington.edu/cgph/centergoals/obesity.htm*).

Technical Assistance
Technical assistance was provided at two events, the Genomics Survey Coordination Workgroup and the Interactive Brown Bag on Public Health Genomics.

Genomics Survey Coordination Workgroup
The UWCGPH established a workgroup of representatives from state health departments interested in collecting data on various genomics-related topics, including family history, through population-based surveys, such as the Behavioral Risk Factor Surveillance System (BRFSS).

The workgroup was comprised of epidemiologists and genomics program coordinators from state health agencies in Michigan, Minnesota, North Carolina, Oregon, and Utah as well as representatives from the CDC Office of Genomics and Disease Prevention (OGDP) and the Centers for Genomics and Public Health. One focus of the workgroup was to evaluate the potential of this population-based data for a variety of public health activities, including:

- Assessing the prevalence of a positive family history of disease.
- Monitoring trends in prevalence of family history of disease.
- Gauging public awareness of family history as a risk factor for disease.
- Tracking provider practices regarding the collection of family history information.
- Understanding how family history contributes to patients' perceptions of risk.
- Investigating beliefs about the ability to modify risk by changing lifestyle factors.

Interactive Brown Bag on Public Health Genomics
In collaboration with the Oregon Department of Human Services (ODHS) Genetics Program, the UWCGPH developed materials for an interactive brown bag session designed to generate interest in genomics for public health audiences. The materials used at the session—including PowerPoint slides, a discussion guide, supplemental reading materials, and an evaluation plan—covered the following six topics:

- Genetic testing for inherited cancer disposition.
- Lifestyle advice.
- Newborn screening.
- Cancer treatment and genetics.

- Workplace testing.
- Reproductive genetics.

These materials have been organized into a package and are available for distribution, although they are not available online. For more information, contact UWCGPH.

Centers' Collaborative Activities with CDC

The three Centers for Genomics and Public Health also worked in collaboration with OGDP to develop an online presentation called Genomics for Public Health Practitioners. This 45-minute presentation is intended for public health practitioners who have minimal experience in genomics and would like to learn more about the relevance of genomics to public health. The program can be accessed at: *www.cdc.gov/genomics/training/GPHP/default.htm*.

The Centers also contributed to a genomics issue of the online Preventing Chronic Disease Journal. Articles can be accessed at: *www.cdc.gov/pcd/issues/2005/apr/toc.htm*.

Summary of the Centers' Activities

The Centers for Genomics and Public Health have become recognized national resources in public health genomics and have increased the capacity of the public health workforce to use genomics information to improve the health of populations. These Centers have established the infrastructure, understanding, and credibility to translate genomics information and discoveries into public health practice and are considered leaders in translating and applying genomic concepts and applications to public health practice.

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Chapter 10

Developing State Capacity for Integrating Genomics into Chronic Disease Prevention Programs: An Update

Introduction

During July 2003, the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) of the Centers for Disease Control and Prevention (CDC) established cooperative agreements with state health departments in Michigan, Minnesota, Oregon, and Utah to strengthen programs for genomics and chronic disease prevention. The purpose of initiating these agreements was to assist states in developing or expanding their capacity for genomics leadership as well as to integrate genomic tools and knowledge into chronic disease programs for improved health outcomes (*www.cdc.gov/genomics/activities/fund2003.htm*).

Accomplishments and Activities for 2004

During January 2004, an initial meeting of the genomics program directors was held in Atlanta, Georgia. The purpose of this meeting was to encourage communication about the progress, plans, and potential collaboration of the four funded states and the three CDC-funded Centers for Genomics and Public Health. *For more information on this topic, see Chapter 9, University Centers for Genomics and Public Health–Michigan, North Carolina and Washington.* One year later, each state has reported the following progress.

Michigan Department of Community Health: Examples of Genomics in Practice

(*www.MIGeneticsconnection.org*)

The goal of the Michigan Department of Community Health (MDCH) Genomics Program is to improve chronic disease prevention efforts and health outcomes through the enhanced use of genomics in core public health functions. The Michigan Genomics and Chronic Disease Prevention cooperative agreement is divided into the following focus areas:

- Michigan Builds a Solid Foundation: Establishing Infrastructure.
- Creating New and Analyzing Old: Using Cancer Registry Data for Genomic Epidemiology.
- Building a Knowledge Base: Increasing Genetic Literacy.

Michigan Builds a Solid Foundation: Establishing Infrastructure
MDCH has increased organizational and operational capacity for integrating genomics into a variety of public health practice activities and selected policy issues. A major accomplishment in 2004 was the creation of the MDCH core genomics team, including permanent state personnel and one contractual employee. A genomics workgroup with representation from each chronic disease program meets quarterly and functions as an extension of the core team.

The MDCH cancer genetics consultant facilitates the Michigan Cancer Genetics Alliance (MCGA). MCGA is a unique statewide public/private partnership with 150 members that provides leadership, education and advocacy for cancer genetics in Michigan (1). The MCGA celebrated its first anniversary in 2004. Major accomplishments of the MCGA include:

- Providing assistance with the development of MDCH cancer risk assessment modules for breast, colon, and prostate cancer.

- Creating an online provider directory and MCGA Web page (*www.migeneticsconnection.org/cancer*).

- Considering Medicare and Medicaid reimbursement for cancer genetic testing.

- Taking initial steps toward collection of statewide data on inherited cancer.

- Creating and disseminating a member newsletter (*www.michigancancer.org/Word/MICaGenAlliance-newsl-Winter04.doc*).

Creating New and Analyzing Old: Using Cancer Registry Data for Genomic Epidemiology
Although family health history is one example of an important genomics tool, the Michigan Genomics program is also exploring other innovative methods of using genomics for chronic disease risk assessment. The Michigan Cancer Registry is a statewide, population-based reporting system that contains cancer incidence and mortality data for reported cases since 1985. Hospitals and laboratories are required by law to file reports on all diagnosed malignant tumors. To determine the feasibility of an inherited cancer surveillance system, multiple genomics projects were initiated in 2004 using the Cancer Registry data, including a review of the following:

- Number of early onset cases (before 50 years of age) by age of diagnosis and age of death for specific cancers (breast, ovarian, colorectal, pancreatic, kidney, stomach and prostate).

- Frequencies of rare malignant tumors with possible hereditary links by **ICD-O** and **morphology codes**.

- Documented family history information by Cancer Registry tumor registrars in abstracted charts at hospitals targeted for quality assurance visits.

Building a Knowledge Base: Increasing Genetic Literacy
Because genomics is a new term, efforts must be made to raise public awareness, stimulate interest, and increase the public's knowledge of this field. In Fall of 2004, the Detroit Science Center hosted the "Genome" exhibit sponsored by Pfizer. For part of this public museum exhibit, the MDCH genomics team members produced a poster exhibit representing genomics and public health through the lifecycle. The genomics coordinator also participated in a daylong event for the public about family history and chronic disease prevention in conjunction with Wayne State University.

In response to the national family health history initiative launched by United States Surgeon General, Dr. Richard H. Carmona (2), the MDCH genomics team created a short electronic newsletter entitled Family History and Your Health. The first in a series, this newsletter was distributed to Michigan public libraries and included a healthy lifestyle message to the public from Michigan's first Surgeon General, Dr. Kimberlydawn Wisdom (3). Librarians expressed great interest in both the newsletter and its message; consequently, libraries will be sent packets of family history and chronic disease prevention information to disseminate to the public.

Minnesota Department of Health (MDH) Chronic Disease Genomics Project: Project Highlights for Year 2004

(*www.health.state.mn.us/divs/hpcd/genomics/index.html*)

The MDH Chronic Disease Genomics Project has focused on the following activities:

- Minnesota Statewide Focus Groups.

- Conference: Genomics and the Connection to Public Health Practice.

- Including genomics in the Minnesota Comprehensive Cancer Control Plan.

- Including genomics in regional chronic disease workshops.

- Genomics presentations at statewide conferences.

ICD-O
The International Classification of Diseases for Oncology is used principally in tumor or cancer registries for coding the site (topography) and the histology (morphology) of neoplasms, usually obtained from a pathology report.

Morphology code
A five-digit code ranging from M-8000/0 to M-9989/3. The first four digits indicate the specific histological term. The fifth digit after the slash (/) is a behavior code that indicates whether a tumor is malignant, benign, in situ, or uncertain.

Minnesota Statewide Focus Groups

An important objective of the Minnesota Department of Health (MDH) Chronic Disease Genomics Project is to develop a sustainable education program on genomics for the public health workforce in Minnesota. To assess need and create a foundation for developing an educational program, the Minnesota Department of Health (MDH) conducted focus groups among key stakeholders throughout the state in May 2004. The purpose of these focus groups was to assess learning needs, priority areas, and concerns among Minnesotans in order to help shape future project activities related to genomics. Five telephone focus groups were conducted with 23 participants from state and local public health departments, healthcare providers, educators, genetic counselors, community leaders, researchers, and healthcare advocates.

The most frequently mentioned issues were:

- Concerns about ethical, legal, social, and public policy issues, including the need for legislator education about these issues.
- Need for education about genomics in health education, health promotion, and disease prevention; health professionals in particular want to integrate practical information about genomics into their activities.
- Capacity building for genomics education, which is perceived as one of the roles for MDH.
- Concern that genomic research will increase health disparities.

When asked what role MDH should play in responding to these issues, participants responded that MDH should:

- Educate a variety of audiences.
- Provide support and technical assistance to public health practitioners for integrating genomics into existing programs.
- Maintain a safe repository for genetic and genomic information.

Overall, the strongest response regarding the role MDH should play was to educate public health practitioners, healthcare providers, legislators, and the public in the following ways:

- Public health practitioners want information regarding practical, cost-effective ways to integrate genomics into their activities, along with easily articulated concepts to explain why genomics are important.

- Health care providers want education regarding family history as a way to stratify risk and make recommendations for screening and testing.

- Participants felt that legislators need accurate information regarding genetic testing and workplace/health insurance issues in order to pass informed non-discrimination laws.

- Practitioners believe the public needs information regarding family health history and balanced, accurate information regarding new discoveries – as opposed to media hype.

The full report can be accessed at *www.health.state.mn.us/divs/hpcd/genomics/*.

Conference: Genomics and the Connection to Public Health Practice
The focus groups conducted in June 2004 helped inform the content and format of Minnesota's first Genomics in Public Health conference held in November 2004. The attendees at this conference were from a wide spectrum of disciplines involved in improving public health in Minnesota.

Three roundtable work groups were held to discuss chronic disease, gene/environment interaction, and ethical, legal, and social issues. The purpose of the roundtables was to identify concrete steps for integrating genomics into public health. Additionally, the participants were asked to complete a survey to define needs and perceptions and concerns related to genomics at completion of the sessions. A report summarizing participant responses helped inform Minnesota's second conference in May 2005. This report is available at: *www.health.state.mn.us/divs/hpcd/genomics/index.html*.

All of the presentations, including a panel discussion and the question and answer session, were video- and audio-taped and recorded on DVD media. The DVDs will be distributed to a variety of audiences in Minnesota and will also be made available online for other audiences. A summary of the conference that includes the conclusions of the roundtable discussions is available at: *www.health.state.mn.us/divs/hpcd/genomics/genomics%20conference%20summary.pdf*.

Genomics Included in the Minnesota Comprehensive Cancer Control Plan
The Minnesota genomics project coordinator co-led a work group to develop strategies for including genomic tools and information in cancer prevention and early intervention activities in the state. Genomic strategies, especially family history and mechanisms for referral and public education, were incorporated as strategies and action steps in all areas of the plan.

At the second Minnesota Cancer Planning summit held in November 2004, action plans were developed for implementing the cancer plan strategies. Family history was identified in many of these action plans as being important in estimating risk, identifying the population burden of cancer and at-risk populations, screening for cancer, and developing prevention and screening messages. The opportunity to integrate genomics in many health care sectors across the state in relation to cancer prevention, screening, and treatment may serve as a model for the integration of genomics in other chronic disease prevention activities. The Minnesota Comprehensive Cancer Plan 2005-2010 is available at *www.cancerplanmn.org/*.

Genomics Included in Regional Chronic Disease Workshops
Minnesota has prepared state plans to address chronic diseases including diabetes, cardiovascular disease, cancer, and arthritis. Representatives from these plans conducted four regional workshops around the state with which to share their plans and encourage partnerships. The Minnesota genomics project health educator was invited to participate in the workshops, which focused on educating and raising awareness of genomics in relation to chronic disease.

The activities consisted of a formal presentation, providing a genomics display with handouts, providing a packet of educational materials, and taking a tour of the various genomic resources and educational tools available online. This was an opportunity to increase capacity and demonstrate the relevance of genomics and family history to chronic disease and to network and build relationships with the public health workforce of Minnesota.

Genomics Presentations at State Professional Conferences
The Minnesota genomics project coordinator and health educator have presented on genomics at several statewide and regional conferences and have received positive reviews. These presentations have addressed genomics and cancer, the role of genomics in preterm labor and birth, nutrigenomics, genomics and MCH issues, and genomics and health disparities. Several of these presentations are available on the Minnesota Chronic Disease Genomics Project website at *www.health.state.mn.us/divs/hpcd/genomics/*.

Oregon State Genetics Program: Genomics and Public Health

(*www.oregongenetics.org*)

The genomics integration effort in Oregon is currently focused on the following activities and goals:

- Integrating genomics into chronic disease programs using the **Stages of Change** model.
- Integrating family history data into population-based surveillance systems.
- Partnering with the Oregon Comprehensive Cancer Control Plan.

Stages of Change (The Transtheoretical Model)
The Stages of Change are different stages that help identify where a person, program or organization is in the process of changing behavior.

Integrating Genomics into Chronic Disease Programs Using the Stages of Change Model

A primary component of the Oregon Genetics Program effort to integrate genomics into public health practice is the creation of a model process to guide integration of genomics into chronic disease program activities. The Genetics Program is currently working with a draft model integration process based on Prochaska and DiClemente's Stages of Change Model, also known as the transtheoretical model (TTM) of behavioral change(4,5). This draft model was created after assessment activities revealed that Oregon's chronic disease programs (e.g., Diabetes, Comprehensive Cancer Control, and Asthma) were at different stages of readiness (i.e., precontemplation, contemplation, preparation, action, or maintenance) to begin using genomics tools in program activities. In the months to come, Genetics Program staff will refine the model and begin working with chronic disease programs to pilot the process.

Integrating Family History Data Into Population-Based Surveillance Systems

This year, Oregon Genetics Program staff added family history-related questions to the 2005 Oregon Behavioral Risk Factor Surveillance System (BRFSS) and the Oregon Toddler Survey (TOTS), a longitudinal follow-up survey to the Oregon PRAMS (Pregnancy Risk Assessment Monitoring System).

The BRFSS family history questions are designed to ascertain health care provider practices and recommendations based on patients' family histories. In addition, questions estimating the prevalence of the population with a family history of diabetes were included. The results will help the Genetics Program work more effectively with health care providers to increase the collection and use of family history information in health care settings. These data will also help identify populations at high or moderate risk of developing diabetes, target public health interventions, and therefore make it possible for the program to use limited resources more efficiently.

TOTS data may be useful in identifying children at increased risk of asthma based on a positive family history. Targeted prevention will then seek to reduce environmental risk factors (such as allergens, cigarette smoke, and air pollutants). TOTS also included questions pertaining to the family history of diabetes. These data will add to knowledge about the relationship between family history of diabetes and risk of developing gestational diabetes.

Collaboration with Oregon Partnership for Cancer Control
The Genetics Program has successfully joined the Oregon Partnership for Cancer Control in the development of the Oregon Cancer Control Plan. Genetics Program staff facilitated the inclusion of genetics information in the Cancer Plan. The population-based focus of the genetics content will be on common, low-penetrance genes that contribute to cancer risk and the interaction of these genes with environmental and behavioral risk factors. The few known cancers that are significantly affected by well-characterized, single-gene mutations (like *BRCA1* and *BRCA2* mutations), will be noted without special emphasis. Family history of cancer will be emphasized as a prevention tool, whereas population-based genetic testing will not. Lastly, the place of appropriate genetic counseling in a comprehensive cancer system will be addressed, as will the ethical, social, and privacy issues surrounding the collection and disclosure of genetic information.

Utah Department of Health: Chronic Disease Genomics Program
(*http://health.utah.gov/genomics*)

The Utah Department of Health (UDOH) Chronic Disease Genomics Program (CDGP) is striving to increase understanding and integration of genomics into public health practice. The CDGP has undertaken a variety of activities to accomplish this goal, including:

- Building public health leadership capacity.
- Educating the public health workforce.
- Exploring the use of family history as a genomic tool.
- Collecting population-based data.

Building Public Health Leadership Capacity
The CDGP has engaged a variety of genetic and public health professionals in developing the leadership necessary for integrating genomics into public health programs. Several strategies have been utilized, including:

- Forming an internal genomics work group consisting of approximately 35 professionals from several departments at the UDOH. Subcommittees have been formed and are implementing work plans related to education, data, and policy issues.

- Forming the external Chronic Disease Standing Committee under the Utah Genetics Advisory Committee to advise the UDOH on genomics policies and activities and update the Utah State Genetics Plan.

- Developing strategies for integrating genomics into the Utah Diabetes Prevention and Control Program, Utah Cancer Control Program, Utah Cancer Action Network, and Utah Asthma Program.

Educating the Public Health Workforce

The CDGP targeted the public health workforce with education and training efforts; the goal of these efforts was to promote understanding of the role of genomics in chronic disease. These education and training activities included the following:

- Assessing genomic knowledge and attitudes as well as appropriate delivery methods of genomics education of 120 UDOH staff.

- Developing and conducting Genomics 101 presentations for approximately 240 public health professionals to increase knowledge and interest levels.

- Drafting a report on current website genomics resources and gaps in those resources for public health professionals as well as for policy makers, health care providers, and the public (6).

Exploring the Use of Family History as a Genomic Tool

The UDOH has extensive experience using family history in chronic disease prevention. From 1983 through 1999, a family history program, the Family High Risk Program (FHRP) or Health Family Tree Project, was used to identify families at high-risk for chronic diseases throughout Utah and provide them with follow-up care.

An assessment was conducted from October 2003 through April 2004 to evaluate the success of the FHRP, during which budgets were reviewed, along with the effectiveness of intervention strategies, perceived successes, barriers and challenges during program implementation, and feasibility of developing new family history programs. Interviews were conducted with former FHRP staff and program materials collected as part of this assessment. A report on the assessment

results was prepared with recommendations for consideration when developing future family history programs, including recommendations for:

- Funding.
- Staff and participant training.
- Partnerships and collaborations.
- Program materials and methods of delivery.
- Legal implications.
- Program leadership.
- Program evaluation.
- Follow-up interventions.

A written report was published on the findings and is available at *http://health.utah.gov/genomics/familyhistory/fhrp.html* (7).

Population-Based Data Collection

The CDGP has assessed or added genomics and family history information to several population-based data collection systems, including:

- *Behavioral Risk Factor Surveillance System (BRFSS)*. Questions were added to assess knowledge, attitudes, and beliefs about the link between family history and disease as well as how much time the public would be willing to spend completing a family history.
- *Utah Population Database (UPDB)*. The UPDB contains genealogy, cancer, driver's license, birth and death, census, and Health Care Financing Administration records. A literature review and discussions with genetic epidemiologists and bioinformatics specialists were held to determine its usefulness for public health genomics.
- *Utah Cancer Control Program (UCCP)* breast and cervical cancer screening enrollment forms. Family history data have been collected by the UCCP for several years; however, it has yet to be analyzed. The data will be analyzed in conjunction with the UCCP to determine the risk ratios for women diagnosed with breast cancer based on a positive or negative family history.

- *Childhood Diabetes Registry* at the Utah Diabetes Center. The registry assesses the incidence and prevalence of diabetes among Utah youth. It contains a section on family history that asks participants, which, if any, first- and second-degree relatives have had diabetes.

Summary of the States' Activities

These four funded states have demonstrated that genomics can be incorporated into public health chronic disease programs. The staff from these states have established infrastructure, built new partnerships, educated the public health workforce about genomics, assessed the integration of genomics into population-based surveillance, and applied family history as a screening tool to identify populations at increased risk of disease in order to more effectively target prevention messages. The progress these states have made and continue to make can serve as a model for other local, state, and regional health departments as they begin to incorporate genomics into public health programs.

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Appendix A

Genomics Internet Resources for Health Professionals

As the information highway continues to expand, Internet resources provide quick and ready access to information for both consumers and health professionals. Although hundreds of websites about genetics and genomics currently exist, the following resources support the chapters covered in this report. Please refer to the disclaimer at the end of this Appendix.

Genomics at CDC	
CDC's Office of Genomics and Disease Prevention (OGDP) *http://www.cdc.gov/genomics/*	This website provides information about human genomic discoveries and how they can be used to improve health and prevent disease. It also provides links to CDC-wide activities in public health genomics across the lifespan.
Public Health Genomics at CDC: Accomplishments and Priorities 2004 *http://www.cdc.gov/genomics/activities/ogdp/2004.htm*	This document, published in January 2005, summarizes CDC's accomplishments, priorities, and future directions in human genomics.
Educational Resources	
Genomics for Public Health Practitioners *http://www.cdc.gov/genomics/training/GPHP/menu_content.html*	A 45-minute introductory presentation on genomics and public health intended for public health practitioners who have minimal experience in the area of genomics as it pertains to public health.

Six Weeks to Genomics Awareness *http://www.genomicawareness.org/index.htm*	An online series of six presentations designed to provide public health professionals a foundation for understanding how genomics advances are relevant to public health.
Genetics Home Reference *http://ghr.nlm.nih.gov/ghr/template/Home.vm*	The National Library of Medicine's website about genetic conditions and the genes responsible for those conditions.
Talking Glossary of Genetic Terms *http://www.genome.gov/10002096*	The National Human Genome Research Institute (NHGRI) created the Talking Glossary of Genetic Terms to help people without scientific backgrounds understand the terms and concepts used in genetic research.
Your Genes, Your Health Multimedia Guide *http://www.ygyh.org/index.htm*	Cold Spring Harbor Laboratory explains genes, health and disease in a multimedia format.
The National Society of Genetic Counselors *http://www.nsgc.org/*	The leading voice, authority, and advocate for the genetic counseling profession.
National Human Genome Center at Howard University *http://www.genomecenter.howard.edu/intro.htm*	The National Human Genome Center at Howard University is a comprehensive resource for genomic research on African Americans.
Genetic Fact Sheets *http://www.genetics.emory.edu/physicians/genetic_fact_sheets.html*	Developed by the Department of Human Genetics, Emory University School of Medicine.

Educational Resources in Spanish

La Oficina de Genómica y Prevención de Enfermedades de los CDC *http://www.cdc.gov/genomics/spanish/default.htm*	Spanish language version of the CDC's Office of Genomics and Disease Prevention website.
Genetica Websites en Espanol *http://www.ornl.gov/sci/techresources/Human_Genome/education/spanish.shtml*	This website from the Department of Energy (DOE) provides information on the Human Genome Project and additional links to Genomics information in Spanish.

International Resources

The WHO Human Genetics Programme *http://www.who.int/genomics/about/en/*	The Human Genetics Programme aims to support international activities on the development of medical genetics services in countries.
Genomics and World Health: Report of Advisory Committee on Health Research *http://www3.who.int/whosis/genomics/pdf/genomics00.pdf*	A 2002 report by the World Health Organization.
Public Health Genetics Unit Newsletter (PHGU), U.K. *http://www.phgu.org.uk/newsletter/newsletter.html*	The PHGU Newsletter contains news about recent research in genetics and its public health implications.

International Genomics Consortium *http://www.intgen.org/index.html*	A nonprofit medical research organization established to expand upon the discoveries of the Human Genome Project.

Family History

CDC's Family History Initiative *http://www.cdc.gov/genomics/activities/famhx.htm*	Provides a description of CDC's Family History Initiative.
CDC's Family History Website for the Public *http://www.cdc.gov/genomics/public/famhistMain.htm*	Provides information for the general public about family history and how it can be used to promote health.
Morbidity and Mortality Weekly Report (MMWR) *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5344a5.htm*	Link to MMWR article, "Awareness of Family Health History as a Risk Factor for Disease—United States, 2004"
U.S. Surgeon General's Family History Initiative *http://www.hhs.gov/familyhistory*	This initiative includes an easy-to-use, downloadable, Web-based family history tool, "My Family Health Portrait".
National Society for Genetic Counselors *http://www.nsgc/consumer/familytree/*	Provides information on how to collect a family history.
National Coalition for Health Professional Education in Genetics (NCHPEG) *http://www.nchpeg.org/nchpeg.html?http://www.nchpeg.org/newsletter/newsletter.asp*	A newsletter for health professionals from NCHPEG's Family History Working group.

Direct-To-Consumer Marketing of Genetic Tests	
Morbidity and Mortality Weekly Report (MMWR) *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5327a1.htm*	Link to MMWR article, "Genetic Testing for Breast and Ovarian Cancer Susceptibility: Evaluating Direct-to-Consumer Marketing - Atlanta, Denver, Raleigh-Durham, and Seattle, 2003."
Marketing of Genetic Tests: Role of FTC *http://www4.od.nih.gov/oba/SACGHS/meetings/October2003/Daynard.pdf*	A PowerPoint presentation from Matthew Daynard at the SACGHS meeting in 2003.
Meeting Summary of Direct to Consumer Advertising of Genetic Tests *http://www.genome.gov/12010660*	Meeting convened by the National Human Genetics Research Institute in March 2004.
Direct-to-Consumer Marketing of Genetic Tests for Cancer: Buyer Beware *http://www.jco.org/cgi/content/full/21/17/3191*	An editorial from the Journal of Clinical Oncology.
Genomics Research	
Human Genome Epidemiology Network (HuGENetTM) *http://www.cdc.gov/genomics/hugenet/default.htm*	A global collaboration of individuals and organizations committed to the assessment of the impact of human genome variation on population health.
Human Genetics and Medical Research *http://history.nih.gov/exhibits/genetics/*	An online exhibit for the public providing information about the use of genetics in medicine sponsored by the National Institute of Health (NIH).

Genes and Populations *http://www.nigms.nih.gov/nes/science_ed/genepop/*	A series of questions and answers for patients considering participation in research studies from the National Institute of General Medical Sciences.
Human Genome Project *http://www.ornl.gov/sci/techresources/Human_Genome/research/research.shtml*	The Human Genome Project was completed in 2003 and this website details the research areas covered by the project.
National Institute of Environmental Health Sciences (NIEHS) National Center for Toxicogenomics (NCT) *http://www.niehs.nih.gov/nct/home.htm*	The NCT mission is to coordinate a nationwide research effort for the development of a toxicogenomics knowledge base.
World Health Organization's Genomics Research Center – Ask the Expert *http://www.who.int/genomics/professionals/GRC_experts/en/*	Send your questions about genomics to members of a judiciously selected group of health professionals in genetics and related disciplines; this group is committed to the development of genomics, public health systems and public engagement in the development of science and technology.
Harvard Medical – Partners Healthcare Center for Genetics and Genomics (HPCGG) *http://www.hpcgg.org/*	HPCGG's mission is to promote genetics and genomics in research and clinical medicine.

Genetic Testing	
Understanding Gene Testing *http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting00.htm*	Provided by the National Cancer Institute, this website illustrates what genes are, explains how mutations occur and how they are identified within genes, and discusses the benefits and limitations of gene testing for cancer and other disorders.
ACCE	
ACCE *http://www.cdc.gov/genomics/activities/fbr.htm*	Conducted by the Foundation for Blood Research under a cooperative agreement with CDC's Office of Genomics and Disease Prevention, the ACCE Project proposed and tested a model process for collecting, evaluating, interpreting, and reporting data about DNA (and related) testing for disorders with a genetic component.
EGAPP	
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) *http://www.cdc.gov/genomics/gtesting/egapp.htm*	EGAPP is a three-year model project launched in 2004 by CDC's Office of Genomics and Disease Prevention. The project's goal is to support the first phases of a coordinated process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice.

Newborn Screening	
Association of Public Health Laboratories (APHL) Newborn Screening and Genetics Program *http://aphl.org/Newborn_Screening_Genetics/index.cfm*	The APHL Newborn Screening and Genetics program strengthens the role of public health laboratories in genetic testing and designs strategies to address changes in the newborn screening field.
March of Dimes Newborn Screening Recommendations *http://www.marchofdimes.com/professionals/682_4043.asp*	Newborn screening recommendations for professionals and researchers.
National Newborn Screening and Genetics Resource Center (NNSGRC) *http://www.genes-r-us.uthscsa.edu/index.htm*	Information and resources on newborn screening and genetics for health professionals, the public health community, consumers and government officials.
Genetic Testing for Rare Diseases	
National Laboratory Network for Rare Disease Genetic Testing *http://www.rarediseasetesting.org/*	A family of laboratories for orphan rare disease diagnostics.
GeneTests/GeneClinics *http://www.genetests.org*	Developed for physicians, healthcare providers, researchers and others to provide information about genetic testing.
National Academy of Sciences: Human Gene Testing *http://www.beyonddiscovery.org/content/view.article.asp?a=239*	A summary of human genetic testing that ranges from the unraveling of the nature of the gene to the social dilemmas posed by genetic testing.

Public Health Practice

CDC-Funded Centers

University of Washington *http://depts.washington.edu/cgph/* **University of Michigan** *http://www.sph.umich.edu/genomics/* **University of North Carolina** *http://www.sph.unc.edu/nccgph/index.htm*	The CDC awarded funding to these three schools of public health, establishing the first "Centers for Genomics and Public Health."

CDC-Funded States

Michigan Department of Community Health *http://www.MIGeneticsconnection.org* **Minnesota Department of Health (MDH) Chronic Disease Genomics Project** *http://www.health.state.mn.us/divs/hpcd/genomics/* **Oregon State Genetics Program** *http://www.oregongenetics.org* **Utah Department of Health (UDOH): Chronic Disease Genomics Program** *http://health.utah.gov/genomics*	CDC established cooperative agreements with state health departments in Michigan, Minnesota, Oregon and Utah to strengthen programs for genomics and chronic disease prevention.

Genes and Diseases	
GDPInfo *http://www2a.cdc.gov/genomics/GDPQueryTool/frmQueryBasicPage.asp*	The GDPInfo query tool allows you to define your search of the OGDP website with a combination of genes, diseases/conditions, topics and other factors.
Genetics Home Reference *http://ghr.nlm.nih.gov/ghr/template/Home.vm*	Genetics Home Reference is the National Library of Medicine's website for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions.
Gene Reviews *http://www.geneclinics.org/servlet/access?id=8888891&key=EU5gttBEabgRZ&fcn=y&fw=wlJK&filename=/home/grcover.html*	An online publication of expert authored disease reviews from GeneTest.
Disease InfoSearch *http://www.geneticalliance.org/DIS/index.html*	Provided by the Genetic Alliance, a tool to assist in finding specific and quality information about genetic conditions.
Websites for Genetic Disorders *http://www.communityschoolhouse.org/websites.geneticdisorders.htm*	More than 20 genetic disorders are listed by the 21st Century Schoolhouse, with links to websites about each disorder.
Genetic and Rare Conditions Website *http://www.kumc.edu/gec/support/*	The Medical Genetics Department of the University of Kansas Medical Center provides links to lay advocacy and support groups along with information on genetic conditions/birth defects for professionals, educators, and individuals.

Ethical and Social Issues

NIH Bioethics Resources *http://www.nih.gov/sigs/bioethics/index.html*	This website contains a broad collage of annotated, comprehensive URLs about bioethics.
Human Genome Project, Ethical, Legal and Social Issues *http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml*	A website sponsored by the U.S. Department of Energy.
Gene-Watch-Council for Responsible Genetics (GRC) *http://www.gene-watch.org/*	Fosters public debate about the social, ethical and environmental implications of genetic technologies.
Center for Genetics and Society/ Human Genetics in the Public Interest *http://www.genetics-and-society.org/index.asp*	A nonprofit information and public affairs organization that works to encourage responsible uses and effective societal governance of the new human genetic and reproductive technologies.
HumGen *http://www.humgen.umontreal.ca/int/GI.cfm*	An international database on the legal, social, and ethical aspects in human genetics.
Ethical, Legal and Social Implications of Genetic Testing: 25 Recommendations from the European Commission (2004) *http://europa.eu.int/eorg/research/conferences/2004/genetic/recommendations_en.htm*	The High Level Expert Group presents twenty-five recommendations on the ethical, legal and social implications of genetic testing.
National Information Resource on Ethics and Human Genetics *http://www.georgetown.edu/research/nrcbl/nirehg/*	A compilation of links, journals and other publications that offer research about ethics and human genetics from Georgetown University.

Policy and Law	
NHGRI Policy and Legislation Database *http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm?CFID=970614&CFTOKEN=58321499*	The National Human Genome Research Institute database contains Federal and State laws/statutes; Federal legislative materials; and Federal administrative and executive materials, including regulations, institutional policies, and executive orders.
National Conference of State Legislatures *http://www.ncsl.org/programs/health/genetics.htm*	Includes table of genetic laws and legislation by state and topic.
Genetics and the Law Project *http://www.genelaw.info/*	An initiative of the Council for Responsible Genetics (CRG), released an expansive, searchable online clearinghouse of information on emerging legal developments in human genetics.
Genetics Policy Database *http://phgu.org.uk/policydb/*	A website from Public Health Genetics Unit (PHGU) listing around 1000 key policy documents in the U.K., from 1984 to the present day.
The Genetic Education Materials (GEM) Database *http://www.gemdatabase.org/GEMDatabase/index.asp*	A searchable listing of public health genetics policy documents and clinical genetics educational materials provided by the National Newborn Screening and Genetics Resource Center.

Genetics and Public Policy Center *http://www.dnapolicy.org/index.jhtml*	Information on genetic technologies and genetic policies for the public, media and policymakers. Funded through a grant from the Pew Charitable Trusts.
GenBiblio *http://www.humgen.umontreal.ca/int/GB_q.cfm*	GenBiblio contains a compilation of policies on human genetics and includes conventions, legislation, declarations, recommendations, guidelines and directives.

Disclaimer: The CDC Office of Genomics and Disease Prevention makes this information available as a public service only. Providing these links does not constitute an endorsement of these organizations or their programs by CDC or the federal government, and none should be inferred. Exclusion of information does not mean there are no other useful resources available. The CDC is not responsible for the content of the individual organization Web pages found at these links. Note that some links may become invalid over time.

Appendix B
Coalition of State Genetics Coordinators

The following list was provided by the Coalition of State Genetics Coordinators (CSGC). The CSGC is an organization of state and territorial genetics coordinators and others who promote core public health functions as they apply to genetics (*http://www.stategeneticscoordinators.org*).

State	Contact Name	Address	Contact Information
AK **Alaska**	Christy LeBlond, MS	State of Alaska, Alaska Genetics Clinic 401 Business Park Boulevard, Building L, Suite 24 Anchorage, AK 99503	(907) 269-3430 (907) 269-3465 fax *Christy_LeBlond@health.state.ak.us*
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CT Connecticut	*Information not available.*		
DC Washington, DC	Michelle C. Sermon	Children with Special Health Care Needs Division Maternal & Family Health Administration 825 North Capitol Street, NE, 3rd Floor Washington, DC 20002	(202) 727-7667 or (202) 727-7449 (202) 727-7789 fax *michelle.sermon@dc.gov*
DE Delaware	Mary Carroll McCaffrey, MS	Delaware Public Health Jesse Cooper Building PO Box 637 Dover, DE 1990	(302) 741-2990 (302) 741-2995 fax *Mary.McCaffrey@state.de.us*
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GUAM	Margaret Lynn Bell	Maternal Child Health Program Department of Public Health & Social Services PO Box 2816 Agana, Guam 96932	(671) 735-7306 direct (671) 735-7305 office (671) 734-2066 fax *mags@kuentos.guam.net*
HI **Hawaii**	Sylvia M. Au, MS, CGC	Hawaii Department of Health 741 Sunset Avenue Honolulu, HI 96816	(808) 733-9063 (808) 733-9068 fax *sylvia@hawaiigenetics.org*
IA **Iowa**	Kimberly Piper	Center for Congenital & Inherited Disorders Iowa Department of Public Health Lucas State Office Building 321 East 12th Street Des Moines, IA 50319	(515) 281-6466
ID **Idaho**	Anne Spencer, MS, CGC	Idaho Department of Health and Welfare Genetic Services Program 2220 Old Penitentiary Road Boise, ID 83712	(208) 334-2235 x 258 (208) 334-2382 fax *SpencerA@idhw.state.id.us*

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IN **Indiana**	Kirstin J. Schwandt, MS, CGC	Genomics & Newborn Screening Indiana State Department of Health 2 North Meridian Street, Section 8C Indianapolis, IN 46204	(317) 233-1268 (317) 233-1300 fax *kschwand@isdh.state.in.us*
KS **Kansas**	Jamey Kendall, RN, BSN	Kansas Department of Health & Environment 1000 SW Jackson Street, Suite 220 Topeka, KS 66612-1274	(785) 296-1316 (785) 296-8616 fax *jkendall@kdhe.state.ks.us*
KY **Kentucky**	Joyce Robl, MPA	Kentucky Department for Public Health Division of Adult and Child Health Improvement 275 E. Main Street, HS 2GW-A Frankfort, KY 40621-0001	(502) 564-2154 x 3768 (502) 564-8389 fax *Joyce.Robl@ky.gov*
LA **Louisiana**	Charles Myers, MSW	Louisiana Department of Health & Hospitals Louisiana Genetic Diseases Program PO Box 60630, Room #308 New Orleans, LA 70160	(504) 568-4033 (504) 599-1376 fax *charlie@dhh.la.gov*

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MT Montana	BJ Archambault, RN	Nurse Consultant Children's Special Health Services PO Box 202951 Helena, MT 59620	(406) 444-0984 (406) 444-2606 fax *barchambault@state.mt.us*
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NJ New Jersey	Kathleen Lutz, MSN, CPNP	New Jersey Department of Health & Senior Services Newborn Screening & Genetic Services Special Child, Adult & EI Services 50 East State Street, 6th Floor PO Box 364 Trenton, NJ 08625-0364	(609) 292-1582 (609) 943-5752 fax *Kathleen.Lutz@doh.state.nj.us*
NM New Mexico	Brenda Romero, RN	New Mexico Department of Health Children's Medical Services 2040 Pacheco Santa Fe, NM 87505	(505) 476-8857 (505) 476-8896 fax *Brenda.romero@doh.state.nm.us*
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OK **Oklahoma**	Pam King, MPA, RN	Oklahoma State Department of Health 1000 Northeast 10th Street Oklahoma City, OK 73117-1299	(405) 271-6617 (405) 271-4892 fax *pamk@health.state.ok.us*
OR **Oregon**	Kiley Ariail, MPH	Department of Human Services State of Oregon 800 NE Oregon Street, Suite 825 Portland, OR 97232	(503) 731-4021 x 304 *kiley.ariail@state.or.us*
PA **Pennsylvania**	Kelly Holland	Pennsylvania Department of Health Bureau of Family Health Division of Newborn Disease Prevention & Identification H & W Building, 7th Floor East PO Box 90 Harrisburg, PA 17108-0090	(717) 783-8143 (717) 705-9386 fax *kholland@state.pa.us*
PR **Puerto Rico**	*Information not available.*		
RI **Rhode Island**			

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We welcome your comments and suggestions about CDC's Genomics and Population Health Report 2005.

Thank you for your response.

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